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CONGRESS ABSTRACTS

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The document provided here is for convenience such that congress attendees can review abstracts before the congress. Abstracts will be published in the journal *Epilepsia* after the congress.
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Platform sessions by session
Tailored epilepsy surgery with high frequency oscillations versus spikes in intra-operative electrocorticography: results of the RCT HFO trial

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Purpose:
Intra-operative electrocorticography (ioECoG) may delineate epileptogenic tissue during epilepsy surgery with higher specificity using high-frequency oscillations (HFOs, 80-500Hz) than using spikes. We prospectively tested the non-inferiority of HFOs to spikes for seizure outcome.

Methods:
This randomized controlled, single-blinded, non-inferiority trial recruited children and adults scheduled for ioECoG-tailored epilepsy surgery (ClinicalTrials.gov:NCT02207673). We excluded patients with occipital foci or chronic invasive EEG. Participants were randomly assigned (1:1) to HFOs (incl. ictiform spike patterns) or spikes, stratified by temporal versus extra-temporal lobe epilepsy (TLE/eTLE). The primary outcome was seizure freedom one year after surgery (Engel 1A-1B). We predefined a non-inferiority margin of 10% absolute risk difference. Analysis was by intention to treat with sub-analyses stratified for epilepsy type. We tested and adjusted for confounders using logistic regression. Secondary outcomes were surgical duration, resection volume, cognition, quality of life, neurological deficits, and serious adverse events.

Results:
Seventy-eight (39/group) patients were enrolled (Oct’14-Jan’20). Seizure freedom occurred in 26 (66.7%) patients in the HFO and 35 (89.7%) patients in the spike group, with an absolute risk difference of -23.5% (90% confidence interval: -39.1 to -7.9), for TLE; -25.5% (-45.1 to -6.0) eTLE; -20.3% (-46.0 to 5.4, N=30). Uni- and multivariable logistic regression revealed poor pathology prognosis as confounder; the adjusted risk difference was: all patients -7.9% (-20.8 to 4.9), TLE -12.5% (-31.0 to 5.9), eTLE -5.8% (-7.7 to 19.5). Secondary outcomes were not different between the groups. We registered eight serious adverse events requiring hospitalization.

Conclusion:
The HFO trial did not demonstrate non-inferiority of HFOs to spikes in ioECoG and suggests superiority of spikes for all patients and the TLE subgroup. These analyses were inconclusive after correcting for poor prognosis as confounder, with non-inferiority of HFOs in eTLE.
Online calculator for seizure freedom following pediatric hemispherectomy: a post hoc analysis of the HOPS study

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**Purpose:** Hemispheric surgeries are one of the most effective procedures for medically intractable epilepsy in the pediatric population, although large variability in outcomes remains. Identifying the ideal hemispherectomy candidates is imperative to maximize the potential for seizure freedom. The objective of this study is to develop an online tool that accurately predicts and reports the probability of seizure freedom for any given patient at 1-, 2-, and 5-years post-hemispherectomy to provide clinicians accessible and reliable prognostic information to complement their clinical judgement.

**Method:** Retrospective data for 1276 pediatric patients from 30 centers internationally was analyzed to determine predictors of seizure freedom following hemispheric surgery. Primary outcomes of interest in this study were the time-to-seizure recurrence and Engel Class (I-IV). A multivariate Cox proportional-hazards regression model was developed to predict the likelihood of seizure freedom post-hemispherectomy based off a combination of statistical analysis and clinical judgement. The final model from this study was developed into a free publicly accessible online calculator that is displayed on the (iNEST) website.

**Results:** The selected variables for inclusion in the final model include the 5 original HOPS variables (age at seizure onset, epilepsy etiologic substrate, generalized seizure semiology, previous non-hemispheric resective surgery, and contralateral PET hypometabolism) and 2 additional variables (contralateral MRI lesion and ictal EEG findings). Significant predictors of shorter time-to-seizure recurrence include younger age of seizure onset, PET hypometabolism contralateral to side of surgery, contralateral MRI lesion, non-lesional MRI, and non-stroke etiologies. The AUC of the final model is 72.9%.

**Conclusion:** Online calculators are efficient, cost-free tools that can facilitate physicians in risk-estimation, inform joint decision-making with families and potentially lead to better long-term seizure freedom in pediatric epilepsy patients. Although the HOPS data was previously validated in the first analysis, the authors encourage further research to prospectively validate this new tool.

Effects of anterior temporal lobe resection on cortical morphology

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**Purpose:** Anterior temporal lobectomy (ATL) is a surgical procedure undertaken to treat medically refractory temporal lobe epilepsy (TLE). We examine and quantify the effects of this major surgical operation on cortical morphology measured in independent variables, both near the resection and remotely.

**Method:** We studied 101 patients with TLE (55 left TLE, 46 right TLE) who underwent ATL. For each we considered one pre-surgical MRI and one scan within one year after surgery. We used our new method to locally compute average cortical thickness, exposed surface area, and total surface area, as well as the independent measures K, I, and S (Leiberg K et al. LNCS 2021;12907:691-700), where K measures white matter tension, I captures isometric scaling, and S contains the remaining information about the shape of the cortex (Wang Y. et al. NeuroImage 2021;226:117546). We controlled for healthy ageing during scans, and used the Matlab toolbox SurfStat (Worsley K et al. NeuroImage 2009;47:S102) for random field theory clustering.

**Results:** We found strong effects of the surgery across the cortex in all variables. Ipsilaterally, the ventrolateral prefrontal cortex changed in all variables but thickness. The pre and post central gyri changed in S, I, and the surface areas for both onset sides, and in right TLE this region also saw changes in thickness and K. In left TLE, K increased in the frontal pole in both hemispheres. In right TLE, all measures but thickness changed in the ipsilateral superior occipital gyrus, and on the contralateral hemisphere we saw increased thickness in the superior parietal lobule, superior occipital gyrus, occipital pole, temporal pole, and middle frontal gyrus.

**Conclusion:** We found strong, widespread effects of ATL to the morphology of the remaining cortex. Specifically, we find evidence for a general restructuration of cortical regions structurally or functionally connected to the resected tissue.
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Why patients with drug resistant focal epilepsy decline further diagnostics and resections following presurgical assessment – a prospective study

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Purpose: In patients with drug-resistant focal epilepsy, epilepsy surgery is the treatment option with the best chance to achieve seizure freedom. Despite this, a high rate of patients declines the recommendation to undergo further invasive video-EEG monitoring (VEM) or resection of the seizure onset zone.

Method: In this prospective study, we included consecutive patients with at least one scalp video-EEG monitoring (sca-VEM) as part of their presurgical assessment performed between 1st of January 2016 and 31st of December 2018. Patients that declined the recommendation to undergo further VEM or resection were asked to provide individual reasons.

Results: Finally, 115 patients with a total of 164 VEMs were further analyzed, 20 patients were eventually found to be ineligible for resection. After sca-VEM, patients received recommendation for either direct resection (n=18), of whom 5 (28%) declined, 25 for VEM with foramen ovale (FO) electrodes, of whom 12 (48%) declined, 48 for intracranial VEM, of whom 17 (35%) declined, and 31 for another sca-VEM, of whom 19 (61%) declined. All patients that received a recommendation for resection after FO or invasive VEM (n=22) agreed to that procedure. The most frequent reasons to decline the physicians’ recommendation for invasive VEM and resections were general fear of brain surgery (51%), followed by currently reduced frequency of seizures (19%), assumed low probability of seizure freedom (15%) and fear of peri- or postoperative complications (15%).

Conclusion: To our knowledge, this is the first prospective study indicating the high rate of patients’ rejections of further diagnostic procedures or resections of the seizure onset zone during presurgical assessment. The main reason for rejections, general fear of brain surgery, may be faced by early consultation of the patients on realistic benefits and risks of resective epilepsy surgery.

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Seizure outcome prediction after pediatric epilepsy surgery: a brain machine learning approach

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Purpose: The use of automated tools predicting outcomes of epilepsy surgery are becoming more popular. Most of these tools use qualitative EEG data and adult patients data. We want to create a model based on an Artificial Neural Network (ANN) that use complex and non linear EEG features to predict seizure outcome after epilepsy surgery in a pediatric cohort.

We calculated predictive accuracy, sensitivity, and precision for each surgery outcome class (seizure free vs non-seizure free).

Methods: We enrolled 124 pediatric patients who underwent epilepsy surgery in our center between 2009 and 2019 with a minimum post-surgical follow-up of 2 years. We extracted preoperative EEG periods of 5-seconds during both resting state period and sleep.

Matlab software was used to design and train the network in a feed forward back-propagation. A combination of EEG features (Power spectrum for each EEG band, Coherence, Entropy, Hjort, Bispectrum, Lyapunove) extracted from each derivation (256 fs) were used to quantify our data. These features were selected by a regression model and only the significant one entered in the ANN model and were used to predict postoperative outcome in 25 patients (subtest-set). To evaluate system accuracy the predicted values were compared with actual outcomes.

Results: EEG parameters predicted seizure outcome with a mean accuracy between 45% and 56%. Statistical analysis used to evaluate the most important predictors of outcome did not show improvement of results.

Conclusion: Our ANN system is an interconnected data mining tool, which prospectively analyzes relationships between electrophysiological variables. The prediction accuracy of 45-56% demonstrate the feasibility of introducing quantitative EEG data in predictive tools based on machine learning. These results are consistent with previously published data. Probably quantitative EEG data should not be used alone as their power is still not sufficient to be used in clinical practice.
Epilepsy surgery in the first six months of life: a systematic review and meta-analysis

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Purpose: Nearly one-third of all infants with epilepsy develop drug-resistant epilepsy. Although epilepsy surgery is a well-established therapy across all age groups, there might beareluctance to operate on infants in the first six months of life due to unique surgical and anesthesiologic difficulties.

Methods: We performed a meta-analysis and systematic review to assess the outcome and complication rate of epilepsy surgery in infants operated on in the first six months of life.

Results: 158 infants underwent epilepsy surgery, most frequently a hemispherotomy rather than focal surgery. Overall seizure freedom after surgery was 65.61% [CI: 0.5785; 0.7261], with higher seizure-free rates following hemispherotomy (71%) than after focal surgery (58%). Complications occurred in 27.65% [0.1794; 0.4004] of patients. Most prevalently, a hydrocephalus developed in 20 out of 136 cases (14.71%). Anti-seizure medication (ASM) could be discontinued in 21.51% [0.1431; 0.3100] and reduced in 85.88% [0.515; 0.9721] of 93 patients postoperatively. 84.61% of infants displayed cognitive impairment (development quotient (DQ) <85) preoperatively. After surgery, there was a trend toward a cognitive gain. However, cognitive gain was seen almost exclusively in seizure-free patients.

Conclusion: Excellent seizure control can be achieved with epilepsy surgery in the first six months of life, a large proportion of patients are able to reduce or discontinue ASM. Data regarding cognitive outcome are promising, but also show that the primary goal should be to achieve seizure freedom. Given the more difficult surgical conditions, epilepsy surgery in the first six months of life should only be performed in specialized epilepsy centers.

Basic science 12:00-13:30 Room A

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Understanding the gene expression diurnal rhythmicity in experimental epileptogenesis

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Purpose: Circadian rhythms are 24-hour endogenous cycles present in virtually all mammalian cells which determine daily changes in physiology and behavior. Although features of epilepsy display strong circadian variation and >80% of protein coding genes display circadian rhythmicity, the chronobiology of epilepsy remains poorly understood at molecular level. Here we sought to identify the impact of epileptogenesis in the diurnal gene expression rhythmicity in mice.

Methods: Next generation RNA sequencing was used to comprehensively characterize the hippocampal gene expression circadian rhythmicity during experimental epileptogenesis. Briefly, wild type adult C57BL/6 male mice (n=5/group; total n=60) underwent intra-amygdala (i.a.) kainic acid-induced status epilepticus (SE) at 8am and 24 hours later had hippocampal samples collected every 4 hours for 24 hours and compared to i.a. PBS-injected control mice collected under the same conditions. Data were analysed with a dedicated circadian rhythm detection tool and an adjusted p-value meta2d_BH.Q<0.001 was considered as significant.

Results: In the hippocampus of control mice were identified 1489 daily oscillating transcripts, while 161 transcripts were oscillating in experimental epilepsy (FDR 0.001). Out of these, only 21 kept oscillating in both conditions and 140 were new rhythms in epileptogenesis. The rhythmicity of most of the genes expressed in control mice was lost in the KA group. Strikingly, 1468 transcripts lost rhythmicity, and SE generated a unique set of rhythmic transcripts not observed in the control mice. Interestingly, 19 out of the 21 overlapping genes between PBS (control) and KA (epileptogenesis) groups were found to have their cycles inverted (significant negative Pearson correlation).

Conclusion: In this pioneer pre-clinical study, we begin to systematically address the dysregulation in diurnal rhythms during epileptogenesis. These vast dataset provides important insights into potential mechanisms that underlie changes in gene expression in epileptogenesis and provide a rationale for pursuing the study of the molecular clock in epilepsy.
Role of myeloid differentiation response 88 protein in seizures and cognition in autoimmune encephalitis

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Purpose: We previously developed a mouse model of seizures in anti-NMDA receptor encephalitis and showed that interleukine-1-mediated signaling is critically involved in the development of autoimmune seizures and associated memory impairment. In the present study we assessed the role of another major inflammatory pathway, the Toll-like receptor (TLR) signaling and myeloid differentiation response 88 (MyD88) protein in generation of seizures and cognitive impairment in encephalitis.

Method: Thirty male and female mice deficient in MyD88, a critical adaptor protein in the TLR pathway, underwent a continuous intracerebroventricular infusion of monoclonal antibodies from a patient with anti-NMDA receptor encephalitis and seizures (n=16) or control antibodies (n=14) for 2 weeks. Their seizure responses were measured with continuous EEG and behavioral tests were carried out to assess motor function, anxiety and memory phenotypes at the conclusion of the antibody treatment.

Results: Only 5 MyD88 knockout mice (31%) exposed to anti-NMDA receptor antibodies developed seizures with the median seizure count of 0 in 2 weeks (interquartile range: IQR 0-1). This was in contrast to 81-94% of wild type mice that were treated with the same antibodies in our previous studies (Taraschenko et al., Epilepsia 2019 60:3, 452-463; Epilepsia 2021, 62:3, 671-682). The MyD88 knockout mice treated with patient antibodies also did not demonstrate anxiety or memory impairment.

Conclusion: MyD88, a major inflammatory signaling protein, is involved in generation of autoimmune seizures and may be potentially targeted for seizure treatment and neuroprotection in encephalitis.

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Hippocampal area CA2 as a novel therapeutic target in epilepsy

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Purpose: The resistance of hippocampal area CA2 to cell death and its hyperexcitability in temporal lobe epilepsy (TLE) is well known, but a possible CA2-based therapeutic strategy hasn’t been tested yet. Here we address the hypothesis that selective inhibition of CA2 pyramidal neurons in a closed-loop fashion during seizures can inhibit abnormal activity in different mouse models of TLE.

Method: To target CA2 pyramidal neurons selectively, we used Amigo2-Cre transgenic mice, in which Cre-recombinase is expressed in CA2 pyramidal neurons. We injected viral vectors expressing the inhibitory opsin archaerhodopsin or eYFP into dorsal CA2 of our intrahippocampal kainic acid (IHKA) and pilocarpine (PILO) mouse models. Next, we implanted a depth opto-electrode in dorsal CA2 and a subdural screw electrode over the frontal cortex. We then configured a closed-loop protocol to detect spontaneous seizures, interictal spikes (IIS), and high-frequency oscillations (HFOs>250Hz) and triggered optogenetic inhibition of CA2 neurons at the time of seizures, IIS, or HFOs. Control experiments used no light stimulation or light stimulation in eYFP-expressing mice.

Results: Real-time detection of IIS with time-locked optogenetic inhibition at the IHKA injection site (n=34) significantly reduced IIS amplitude vs. no stimulation (n=175) or stimulation in eYFP-expressing mice (n=23). A similar suppressive effect was found in the PILO model. In both TLE models, convulsive seizures were significantly shorter using optogenetic stimulation (30.6±2.9s) compared to no stimulation (51.2±2.0s; p<0.001, n=3 mice). Notably, we were able to silence HFOs occurring in slow-wave sleep in both TLE models (n=4 mice).

Conclusion: Our results using closed-loop optogenetic silencing of seizures, IIS, and HFOs in 2 TLE mouse models suggest that area CA2 could be a novel therapeutic target in TLE. Considering the survival of CA2 in TLE and its important role in healthy individuals, our results may lead to ‘CA2-specific’ pharmacotherapies for seizures, their biomarkers, and comorbidities.
**Investigation of second hit hypothesis in DEPDC5 and TSC double mutant zebrafish: a phenotypic and transcriptomic analysis**

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**Purpose:** mTORopathies are a group of neurodevelopmental diseases driven by mTORC1 hyperactivity resulting in focal malformations of cortical development (FMCD) and epilepsy. Despite common molecular and clinical features, the severity of the disease varies strongly, even intrafamilial. The second hit hypothesis proposes that an additional, inactivating mutation in the remaining functional allele causes a stronger phenotype and therefore explains the phenotypic variability. Recently, second hit mutations have been detected more frequently in mTORopathies. Nevertheless, their impact on FMCD and epilepsy is poorly understood.

**Method:** We generated a second hit zebrafish model by combining *tsc2* and *depdc5* loss of function and investigated the pathophysiological effects of second hit hypothesis on brain anatomy and epilepsy phenotype. Furthermore, underlying clinically relevant mechanisms were unraveled by RNA sequencing.

**Results:** Loss of *tsc2* and *depdc5* resulted in strongly increased levels of mTORC1 activity (p<0.0065) and earlier lethality (p<0.000001) in second hit zebrafish, which could be reversed by rapamycin. Despite alterations of eye, jaw and abdominal size, brain size of second hit zebrafish was surprisingly not altered. Moreover, cell size and amount of cells in their brain was unaffected and only subtle anatomic abnormalities (dilatation of brain ventricles) were detected. In behavioral and electrophysiological assays, second hit zebrafish displayed hypactivity (p<0.001) and importantly increased seizure susceptibility (p=0.0277). RNA sequencing revealed a high amount of differentially expressed genes (9349 DEGs) in second hit zebrafish with many genes related to neurodevelopmental processes being down-regulated and mitochondrial genes being up-regulated. Finally, overlap of the transcriptomic profile of second hit zebrafish with human SEGA lesions identified mitochondrial-related pathways as significantly dysregulated (p<1.427117e-05). Importantly, mitochondrial abnormalities could also be found by electron microscopy.

**Conclusion:** This study addresses the phenotypical hallmarks of a second hit mutation in zebrafish and suggests a role for mitochondrial abnormalities in mTORopathies.

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**Closed-loop control of neuronal network excitability using adenosine photopharmacology**

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**Purpose:** Adenosine A1 receptors (A1Rs) inhibit neurotransmission and neuronal excitability through Gi-signaling. They are a promising therapeutic target for epilepsy but are ubiquitously expressed throughout the body and therefore would need to be activated locally in the brain to avoid side effects. Photopharmacology allows site-specific receptor activation using light-sensitive caged compounds. We report the use of a novel photocaged A1R agonist to achieve targeted inhibition of hippocampal networks in control and hyperexcitable conditions.

**Method:** The photoactive A1R agonist was synthetized by conjugating diethylaminoucoumarin-4-yl)methyl (DEACM) to the secondary amine group of N6-Cyclopentyladenosine (CPA). To validate light-triggered activation of this DEACM-caged CPA (cCPA), ex vivo rat hippocampal slices were incubated with 3 μM cCPA and exposed to 4 mW pulses of 405 nm light (500-2000 ms) while CA1 evoked potentials (EPs) were measured. Next, light pulses (25/50 ms) were administered each time EPs increased above a preset amplitude level, thus constituting a photopharmacology feedback system. This photopharmacology approach was tested in vivo in mice by injecting 5 µl of 33 mM cCPA intraventricularly and exposing the dentate gyrus (DG) to 8 mW pulses (100 ms, 0.1 Hz) of 405 nm light while recording DG EPs.

**Result:** Light-triggered uncaging of cCPA resulted in potent suppression of neurotransmission and excitability with an induction time in the seconds range and a recovery rate in the minute range, reflecting the underlying Gi signaling. The feedback system allowed to control EP amplitude even in conditions of hyperexcitability, otherwise resulting in large EP increases and epileptic bursting. In vivo uncaging of cCPA resulted in potent inhibition of DG EPs.

**Conclusion:** Combining EP as biomarker for network excitability with an innovative photocaged A1R agonist could allow to setup a feedback control system that keeps excitability of seizure networks below seizure threshold while preserving normal synaptic function.
Reflections of very high-frequency oscillations (>500Hz) in routine stereo-EEG

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Purpose: The aim of the study was to investigate intracranial stereo-EEG (SEEG) recorded in patients with drug-resistant epilepsy. Recently, very high frequency-oscillations (VHFOs, >500 Hz) might be more specific in localizing the epileptogenic zone, than high-frequency oscillations (HFOs, <500 Hz). However, to measure VHFOs, immense sampling frequencies of SEEG recordings are necessary (Usui N et al. Annals of neurology 2015;78.2: 295-302; Brázdil M et al. Annals of neurology 2017;82.2:299-310). The focus was to investigate possible reflections of the VHFOs in the recordings undersampled to 1 kHz. We hypothesized that it is possible to distinguish SEEG undersampled signals with or without the presence of VHFOs.

Method: The initial cohort of patients included 67 adult patients with drug-resistant epilepsy who underwent SEEG and surgery with ≥2 years follow up. 13 patients met the criteria for further analysis of VHFOs: good outcome Engel IA or IB, localized seizure onset zone and its overlap with resection, implanted hippocampus, and detected VHFOs. 5 kHz recordings from 141 SEEG contacts were manually classified into RED (channels with HFOs and VHFOs = 50) and GREEN (channels with HFOs and without VHFOs = 91) contacts. Undersampled 1 kHz were analyzed based on the calculated maximum of absolute amplitude, 75th percentile of power spectral density estimate, Shannon entropy, and Teager-Kaiser energy operator.

Results: The p values of calculated features of RED and GREEN contacts with 1 kHz sampling frequency were all p < 0.0001 (corrected for multiple comparisons). Further, the p values of ripple and fast ripple rates calculated from the original 5kHz contact recordings were p = 0.4795 and p = 0.7237.

Conclusion: Our results suggest that VHFO reflections can be found in recordings with sampling frequency of 1kHz and thus classify recordings pre-examined for HFOs into GREEN and RED SEEG contacts.

Clinical Neurophysiology 1 12:00-13:30
Sunday, 10 July 2022 Room X

Open access EEG data via DICOM standard

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Purpose: To discuss and promote a unified standard format for EEG and other neurophysiological data (DICOM) to improve clinical care and fuel future research, which rely on data exchange.

The ability to access and share EEG data between different healthcare providers is currently limited due to a myriad of different file formats and proprietary access protocols used by manufactures of EEG equipment. No unified and clinical established EEG data format with the ability for long-term storage in current hospital data systems is used today. Access to legacy EEG data, especially with rare pathologic activity such as seizures, would be invaluable for healthcare providers, researchers and patients due to several reasons: 1) improved analytical EEG methods that increase diagnostic yield; 2) new therapeutic options in the future which use EEG biomarkers; 3) differential diagnosis or reassessment of initial diagnosis if a specific therapy is unsuccessful (Halford JJ et al. Clin Neurophysiol 2021; 132(4):993-7).

Method: To implement a standardized format in neurophysiology, the DICOM Working Group 32 was established in 2018 (https://www.dicomstandard.org/activity/wgs/wg-32). DICOM offers an ideal environment to achieve neurophysiology format standardization because neurophysiological data can be easily integrated with existing DICOM-supported elements such as video, ECG, and images. It also provides easy integration into existing hospital PACS long-term storage systems.

An ongoing pilot project was established in June 2019 consisting of an automated workflow which archives long-term EEG monitoring data after review into the existing data storage system of public hospitals in Vienna.

Results: 123 individual long-term EEG monitoring sessions were successfully archived and 100% could be retrieved and read via a DICOM EEG review software (Encevis).

Conclusion: Our pilot project showed that a workflow of automatically archiving long-term EEG monitoring data after review and their storage as well as access via existing data storage systems of public hospitals is feasible.
Detecting interictal discharges in ultra long-term subcutaneous electroencephalography

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Purpose: Interictal epileptiform discharges (IEDs) are used as an important biomarker of epilepsy. The gold standard for annotating IEDs in electroencephalography (EEG) is a manual, time-consuming process with a low inter-rater agreement. Multiple algorithms have been proposed to automate the annotation process for scalp EEG, but a generic algorithm has not been developed for ultra long-term EEG with few electrodes. We set out to develop a generic IED detection algorithm for data measured with the 24/7 EEG™ SubQ solution from UNEEG medical.

Method: Subcutaneous EEG from 10 different people with epilepsy and eight healthy controls were used. To enrich the data with IED annotations, a detection algorithm was adapted. It was iteratively trained on existing IED annotations together with EEG from the healthy subjects and then applied to unseen data. In each iteration, new detections were approved or rejected by medical doctors and inserted into the data set. A total of 1248 IEDs were found. Another algorithm was adapted, modified (Perslev et al., Adv. Neural Inf. Process. Syst. 2019;32:1-19) and trained in a leave-one-subject-out cross-validation scheme. For each fold, it was tested on an EEG segment (>6h) from the left-out subject containing at least 10 IEDs.

Results: There were ~39 hours of test data with 287 approved IEDs. An average sensitivity of 90 % was achieved. The average number of false positive per hour was ~31, but this number should be carefully interpreted as false positives could be IEDs not yet presented to a medical doctor.

Conclusion: Our results show that a generic algorithm can find IEDs in ultra long-term recordings made with the UNEEG SubQ solution. In future work the algorithm should be evaluated on an independent, manually annotated test set.

Funds statement: AWH and JDH are employees at UNEEG medical A/S and TWK consults for the company.

Brain networks functional connectivity changes after stereotactic thermocoagulation in drug-resistant epilepsy patients

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Purpose: Stereoelectroencephalography-guided radiofrequency thermocoagulation (SEEG-guided RF-TC) aims at reducing seizure frequency in drug-resistant epileptic patients (DRE), by creating local thermocoagulative lesions in the epileptogenic areas. Although RF-TC is hypothesized to functionally modify the epileptogenic network, accounts for functional connectivity (FC) changes are missing. We evaluated, by means of SEEG recordings in DRE patients, whether variations of brain activity after RF-TC (at the network and local level) are related to clinical outcome.

Method: Interictal SEEG recordings from 34 DRE patients (17 responders and 17 non responders) were analysed before and after RF-TC. The local (power spectral density, PSD) and FC changes were evaluated in three-minutes-long segments of recording before and 15 minutes after RF-TC. FC was evaluated via the non-linear regression coefficient h². The PSD and h² strength values after thermocoagulation were compared with baseline.

Results: In responders, thermocoagulated contacts showed a significant reduction of PSD after RF-TC, which was significantly different from non-thermocoagulated contacts for all bands (delta: p=0.002, theta: p=0.006, alpha, beta, low gamma: p=0.04). In contrast, no differences were found in PSD changes between thermocoagulated and non-thermocoagulated contacts in non-responders. At the network level, the FC strength value changed after RF-TC for the delta (p=0.01), beta (p=0.001) and broad (p=0.02) bands between the responder and the non-responders group. These differences were specific to the thermocoagulated areas only. Indeed, the FC strength variation of thermocoagulated contacts in responders was significantly different from the one in non-responders (delta: p=0.002, alpha: p=0.009, beta: p=0.0001, broad: p=0.04).

Conclusion: Thermocoagulative lesions induce local and network FC changes in brains of DRE patients lasting for at least 15 minutes. Importantly, differences in brain network activity are observed between responders and non-responders. These results open new perspectives for the investigation of longer-lasting FC changes after RF-TC.
A retrospective study of the correlation between duration of monitoring in epilepsy monitoring unit and diagnostic yield

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Objective: Long-term video electroencephalographic (vEEG) monitoring is a valuable tool in the evaluation of paroxysmal clinical events. However, vEEG itself is costly. Hence, we aimed to establish whether longer duration of monitoring (DOM) is associated with higher diagnostic yield.

Method: A retrospective review of patients admitted to the epilepsy monitoring unit (EMU) for the diagnostic evaluation of paroxysmal events was performed. Patients' demographic, clinical and vEEG data were analysed. The odds ratio of achieving diagnostic studies was generated by comparison of odds between DOM ≤7 days versus >7 days. For patients with DOM >7 days, the reasons for prolonged DOM were identified and the differences in clinical characteristics and vEEG data between diagnostic and non-diagnostic studies were analysed.

Result: A total of 501 patients was included. Four hundred and thirty-six (87%) patients had diagnostic studies. Of these, 67.9% patients with diagnostic studies received diagnosis within the first 7 days of monitoring with the highest during day 7. The odds ratio of diagnostic studies decreases with additional days of vEEG beyond 7 days. A total of 175 had DOM >7 days of which 80.1% were diagnostic. In cohort with DOM >7 days, patients with previous abnormal routine EEG, previous vEEG monitoring, first event recorded before day 5 of admission and more number of events were more likely to have diagnostic studies. The most common reason for DOM >7 days was the need to record more events (76%).

Conclusion: Our study supports that longer DOM was associated with an increase in diagnostic yield. More than one third of our cohort were monitored beyond 7 days with majority of these (80.1%) were diagnostic. Our findings may guide clinicians in planning DOM and predicting likelihood of diagnostic vEEG studies in patients with prolonged DOM based on clinical characteristics and vEEG data.

Is ultra long-term subcutaneous EEG a game changer in future management of epilepsy?

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Purpose: Despite their known inaccuracy, self-reported epileptic seizure diaries are the current standard in clinical practice to estimate seizure burden of people with epilepsy (PWE) and to guide their treatment. Ultra long-term monitoring with subcutaneous EEG (sqEEG) offers a novel, minimally invasive and objective alternative to record electrographic seizures in real-life settings. To justify the minimally invasive sqEEG-based solution over the self-reported diaries, we carried out comparison analyses.

Method: The sqEEG solution was applied for epileptic seizure monitoring throughout 2-3 months in nine people with drug resistant, temporal lobe epilepsy. During the recording period, the PWE were keeping manual seizure diaries. The total of 490 days of sqEEG recordings were reviewed and labelled manually by three independent clinical experts (94 agreed electrographic seizures). Cohen’s kappa statistic was calculated to determine the degree of agreement between the self-reported diaries and the electrographic seizures. Assessments were included to determine whether the sqEEG-based solution brought clinical value for each PWE.

Results: The agreement between the diary and the electrographic seizures were low (kappa < 0.6) for all but one PWE (median: 0.29; range: 0 - 1.0). The sqEEG-based solution was considered to add solid clinical value for six out of eight PWE, both shedding light on potential under- and overreporting in the self-reported diaries.

Conclusion: In comparison with self-reported seizure diaries, six of eight PWE were considered examples of clinical cases where the objective sqEEG-based seizure monitoring would provide valuable insights to optimize epilepsy treatment strategy. Thus, in combination with a process of automatic seizure detection/review to reduce the extensive workload of manual seizure labelling of ultra long-term data, the sqEEG-based solution could be a game changer in future management of epilepsy.
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Contribution of cortico-cortical evoked potentials in the localization of the seizure-onset zone during stereo-electroencephalography

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Purpose: Single-pulse electrical stimulation (SPES) is used during intracranial EEG to improve the seizure-onset zone (SOZ) localization. Different evoked responses, including cortico-cortical evoked potentials (CCEPs), have been used to identify eloquent cortical areas and the SOZ. This retrospective study aims at assessing if a connectivity index, based on CCEPs, can contribute to SOZ localization in stereo-electroencephalography (SEEG).

Method: Five patients (2F; age, mean: 24y, range: 16-44y, with 1 to 5 years post-resection seizure-freedom) underwent SPES (9mA, 0.9Hz, 70mV, 120s, 100 bipolar stimulations) during SEEG. CCEPs were averaged and permutation tests were used to assess their significance. A connectivity index (CI; Yan et al., J Neurosurg 2019) assessed epileptogenicity at each stimulated electrode eliciting significant CCEPs. CI is the number of electrodes recording significant CCEPs multiplied by the Euclidian distance of each electrode with the stimulated electrodes, divided by the number of recording electrodes multiplied by the Euclidian distance of each of them with the stimulated electrodes. According to Yan et al. (2019), CI>0.30 is indicative of SOZ (sensitivity: 0.92, specificity: 0.70), while CI<0.19 is indicative of non-epileptic sites (sensitivity: 0.71, specificity: 0.92).

Results: 193 SPES were performed (19-75/patient), 20 in the SOZ (2-5/patient). CI>0.30 and <0.19 were found both inside and outside the SOZ (CI>0.30: sensitivity: 0.43, specificity: 0.88 for SOZ; CI<0.19: sensitivity: 0.27, specificity: 0.81 for non-SOZ sites). The highest values of CI (> 0.90) were found outside the SOZ.

Conclusion: The CI characterizing CCEPs after SPES, described as an effective metric for grading epileptogenicity in electrocorticography, does not contribute to SOZ localization in SEEG. This could be due to different spatial brain sampling. SEEG allows investigation of polysynaptic neural connectivity and accurate sampling of deep anatomical areas, and electrocorticography allows investigation of wide gyral surfaces. Furthermore, epileptogenicity could not be due only to high connectivity.

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Psychological assessment prior to and after switch from levetiracetam to brivaracetam: a controlled questionnaire study

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Purpose: In clinical practice, brivaracetam (BRV) sometimes replaces levetiracetam (LEV) due to the inadequate response or adverse events of LEV in people with epilepsy (PWE). This study evaluated psychological changes in patients with epilepsy who were switched immediately from LEV to BRV in comparison to patients with unchanged LEV. We suggested a possible beneficial response in some PWE according to psychological measures.

Method: To evaluate psychological changes in patients with epilepsy who switched from LEV to BRV and unchanged LEV we used multiple psychological tests such as SCL-90-S, BDI II, AEP and Qolie-31-P. Eligible participants completed the questionnaires at baseline and again 7 days later. Psychological changes were assessed using standard statistic methods to show differences between a group switched from LEV to BRV and another group with unchanged LEV.

Results: 63 in-patients participated, of whom 34 were switched to BRV. At baseline, participants who switched to BRV had a smaller number of antiseizure medications (2.1 vs 2.6, p=0.029) but a higher number of seizures per months (p=0.026 for focal seizure, p=0.015 for bilateral tonic-clonic seizures). Among all psychological tests at baseline, only scores for anxiety (p=0.020) and psychoticism (p=0.046) in PWE switched to BRV were higher than in the control group. In the second assessment one week later, all psychological scores were not significantly different in both groups anymore. The multiple regression indicated that male gender, younger age, and monotherapy were significant predictors of psychological improvement. No adverse event occurred during the study.

Conclusion: Despite a short period of observation, this study shows psychological improvement after switching from LEV to BRV in some PWE. LEV can be safely switched to BRV in epilepsy patients having psychological adverse events.
A cohort study of pyridoxine or pyridoxal-5-phosphate treatment for seizures in glycosylphosphatidylinositol deficiency

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Purpose: We aimed to explore the efficacy and safety of high-dosage pyridoxine and pyridoxal-5-phosphate (P5P) in the treatment of epilepsies related to congenital glycosylphosphatidylinositol deficiency. We used seizure frequency reduction and EEG improvements as primary treatment outcomes.

Methods: We treated patients with genetically confirmed congenital glycosylphosphatidylinositol deficiency with oral pyridoxine or P5P. This was done as compassionate use in an agreed-upon clinical regimen. Pyridoxine (20-30 mg/kg per day) was used for 3 months. A baseline evaluation included one video-EEG and four weeks of prospective and daily seizures registration. The daily registration of seizures continued during the pyridoxine and P5P intervention. Once maximal dosage of pyridoxine was reached, the EEG was repeated. If the burden of seizures was unchanged after 3 months of treatment, pyridoxine was replaced by P5P (20-30 mg/kg per day). The P5P intervention lasted another 3 months and ended with a follow-up EEG.

Results: We included eight patients with PIGA-, PIGT-, or PIGV-related glycosylphosphatidylinositol deficiency. All suffered from developmental and cognitive impairment as well as treatment resistant seizures. One patient became seizure free while >50% seizure frequency reduction was reported in 2/8, and <50% reduction in another 3/8. We observed no electrophysiological changes in 6 out of 8 patients during intervention when comparing baseline and follow-up EEGs.

Conclusion: Pyridoxine may reduce burden of seizures in congenital glycosylphosphatidylinositol deficiency. We observed no long-lasting electrophysiological improvements during treatment.

Long-term perampanel monotherapy and health-related quality of life in patients with newly diagnosed/currently untreated recurrent focal-onset seizures: FREEDOM study 342 extension phase

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Purpose: FREEDOM (NCT03201900) was a multicentre, Phase III, open-label study of perampanel monotherapy in patients aged ≥12 years with newly diagnosed/currently untreated recurrent focal-onset seizures (FOS), with/without focal to bilateral tonic-clonic seizures. We report health-related quality of life (HRQoL) data from FREEDOM as measured by the EuroQol 5-Dimension 5-Level (EQ-5D-5L) questionnaire.

Method: During the Core Study, patients received perampanel 4 mg/day (4-week Pretreatment [baseline]; 32-week Treatment [6-week Titration; 26-week Maintenance] with the possibility to up-titrate to 8 mg/day). Patients could enter an Extension Phase for an additional 26 weeks (total: 52 weeks). Seizure freedom was the primary endpoint (modified Intent-to-Treat [mITT] Analysis Set). Exploratory endpoints included EQ-5D-5L assessed in mITT across five domains (mobility, self-care, doing usual activities, pain/discomfort, and anxiety/depression) and change from baseline to End of Treatment (EoT; including Extension Phase) in the EQ-5D-5L; EQ visual analogue scale (VAS) was also assessed.

Results: Overall, 89 patients received ≥1 perampanel dose; 73 patients entered the 4-mg/day Maintenance Period (mITT Analysis Set); 21 patients entered the 8-mg/day Treatment Phase. Forty-six patients entered the Extension Phase. Of 39 patients who entered the Extension Phase while seizure free, 31 (79.5%) patients had sustained seizure freedom for 52 weeks. At EoT, ≥77.5% of patients reported no problems across EQ-5D-5L domains. Overall, ≥60.6% of patients had no change, 2.8–21.2% showed an improvement and 7.0–18.3% had a worsening of problems across EQ-5D-5L domains at EoT respective to baseline. Change in EQ VAS from baseline to EoT (mean [standard deviation], 0.9 [15.4]) suggested that there was no change in the self-perceived health of patients.

Conclusion: These data indicate that long-term perampanel monotherapy 4-8 mg/day is effective at sustaining seizure freedom and does not negatively affect HRQoL, with some patients showing an improvement in HRQoL across the domains.

Funding: Eisai Inc.
Safety, pharmacokinetics (PK), and cerebrospinal (CSF) exposure data from the ongoing Phase 1/2a MONARCH study of STK-001, an antisense oligonucleotide (ASO), in children and adolescents with Dravet syndrome (DS)

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Purpose: DS is a severe and progressive genetic epilepsy that is generally caused by spontaneous, heterozygous loss of function mutations in the SCN1A gene, which encodes the voltage-gated sodium channel subunit type 1 α (Na1.1). STK-001 is an investigational ASO designed to upregulate Na1.1 protein expression in brain by leveraging the wild-type (non-mutant) copy of SCN1A to restore physiological Na1.1 levels, thereby potentially reducing seizure frequency (SF) and non-seizure comorbidities.

Method: Patients (N=22) with DS were grouped by age (2-12 and 13-18 years) and SF was evaluated for 28 days before CSF collection (baseline). During the pre-treatment period, patients had a high rate of convulsive SF (median=16). STK-001 was administered intrathecally on Day 1 as a single dose (SAD: 10, 20, or 30mg) or on Day 1, Week 4 and Week 8 as multiple ascending doses (MAD: 20mg).

Results: 20/22 patients were taking ≥3 concomitant anti-seizure medicines as maintenance therapy, and 16/22 were taking ≥4. Adverse events (AEs), SF, and plasma PK were monitored throughout. At datacut, 4 patients had study drug-related treatment-emergent (TE) AEs; none in 30mg SAD and 1 in the 20mg MAD cohorts. Five patients had serious TEAEs, none related to study drug. In addition, 12/17 SAD patients experienced a reduction in convulsive SF from Day 1 to Days 29-84, including 7/7 in the 2-12 years age group. Dose-dependent increases in plasma exposure were observed and STK-001 could be measured in the CSF up to 6 months post single intrathecal dose.

Conclusion: Single doses of STK-001 up to 30mg, and three 20mg doses of STK-001 given every four weeks, were well-tolerated with no study drug-related safety concerns observed. This MONARCH data analysis provides positive safety and PK data and evidence of seizure reduction, supporting continued development of STK-001 as the first disease-modifying precision medicine for DS.
Real-world experience of perampanel monotherapy in epilepsy patients with focal-onset and generalised-onset seizures

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Purpose: To assess the real-world effectiveness and safety/tolerability of perampanel (PER) when used as monotherapy in everyday clinical practice.

Method: Patients treated with PER monotherapy (first-line or conversion to monotherapy) for focal-onset and/or generalised-onset seizures were identified from a pooled analysis of 44 prospective/retrospective/cross-sectional clinical practice studies. Retention was assessed after 3, 6 and 12 months of PER treatment. Effectiveness assessments comprised seizure freedom rate (no seizures since at least the prior visit) and responder rate (≥50% seizure frequency reduction), assessed by seizure type at the last visit (last observation carried forward). Adverse events (AEs), psychiatric AEs, and AEs leading to discontinuation were evaluated.

Results: Overall, 268 patients received PER monotherapy at baseline (mean epilepsy duration, 13.2 years). Seizure types at baseline were focal-onset only (75.0%), generalised-onset only (24.5%), and focal-onset and generalised-onset (0.5%). Mean PER doses at baseline and last visit were 3.0 and 5.5 mg/day, respectively. Mean number of antiseizure medications (ASMs) given prior to PER monotherapy was 2.7. At the last visit, 30.8% of patients were treated with concomitant ASMs. At 3, 6 and 12 months, retention rates were 91.1%, 87.3% and 73.3%, respectively. Mean time under PER treatment was 11.9 (11.5–12.3) months. At the last visit, seizure freedom rates in patients with focal-onset and generalised-onset seizures were 64.1% and 69.4%, respectively; corresponding responder rates were 84.4% and 93.9%, respectively. AEs were reported for 45.2% of patients, with the most frequent (≥10% of patients) being dizziness/vertigo (16.8%) and irritability (11.2%); 13.7% of patients discontinued due to AEs over 12 months. Psychiatric AEs were reported for 20.8% of patients.

Conclusion: In everyday clinical practice, PER was effective and generally well-tolerated when used as monotherapy for focal-onset and/or generalised-onset seizures. At the last visit, approximately two-thirds of patients were seizure free. Supported by Eisai

Perampanel for the treatment of patients with idiopathic generalised epilepsy in clinical practice

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Purpose: To assess the real-world effectiveness, safety and tolerability of perampanel (PER) when used to treat patients with idiopathic generalised epilepsy (IGE) in everyday clinical practice.

Method: Patients with IGE were identified from a pooled analysis of 44 prospective, retrospective and cross-sectional PER clinical practice studies/work groups. Retention was assessed after 3, 6 and 12 months of PER treatment. Effectiveness assessments comprised responder rate (≥50% seizure frequency reduction), seizure freedom rate (no seizures since at least the prior visit), and proportions of patients with unchanged or worsening seizure frequency. Safety and tolerability were assessed by evaluating adverse events (AEs), psychiatric AEs, and AEs leading to discontinuation.

Results: Overall, 540 patients with IGE were identified. Seizure types at baseline included generalised tonic-clonic, myoclonic, absence and combinations of these. Mean (standard deviation) PER dose was 2.5 (1.2) mg/day at baseline and 5.6 (2.4) mg/day at the last visit (last observation carried forward). Retention rates at 3, 6 and 12 months were 92.3%, 85.4% and 77.4%, respectively. Reasons for discontinuation were AEs (11.3%), lack of efficacy (6.0%), and both AEs and lack of efficacy (1.0%). Mean (95% confidence interval) time under PER treatment was 11.9 (11.5–12.3) months. At the last visit, responder and seizure freedom rates were 74.2% and 54.6%, respectively; and the proportions of patients with unchanged and worsening seizure frequency were 11.3% and 5.9%, respectively. AEs were reported for 42.8% of patients and psychiatric AEs were reported for 21.8% of patients. The most frequently reported AEs were irritability (14.5%), dizziness/vertigo (11.6%) and somnolence (9.9%). At 12 months, 12.3% of patients had discontinued due to AEs.

Conclusion: PER was effective and generally well tolerated when used to treat patients with IGE in everyday clinical practice. At the last visit, over 50% of patients were seizure free. Supported by Eisai
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A library of quantitative markers of seizure severity: distinguishing between seizure types and detecting circadian modulation

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Purpose: Current gold standards for assessing the severity of an epileptic seizure are based on ratings from patients and clinicians. However, automated, quantitative approaches are desirable for a range of applications including, but not limited to, chronic monitoring, seizure prediction and closed-loop treatment approaches. Therefore, we developed a library of quantitative EEG markers to assess the spread and intensity of abnormal electrical activity during seizures.

Method: Intracranial electroencephalographic (iEEG) recordings from 63 patients were retrospectively obtained and analysed. Each of the 14 markers of seizure severity introduced within this paper were validated with ILAE seizure type classifications to determine if they can successfully distinguish clinical seizure types. Differences between severity markers for FTBTCS, focal and subclinical seizures were investigated on a within-patient and across-patient basis. Circadian rhythms in seizure severity markers were investigated on a within-patient basis as a further validation.

Results: Across all patients and accounting for patient-level effects, all markers of seizure severity could distinguish focal and subclinical seizures, whilst 11 could distinguish FTBTCS and focal seizures. In individual patients, Wilcoxon rank sum tests found that for 50% of patients there was a moderate to large difference detected between focal and subclinical seizures in two or more markers. Periodic regression models found significant circadian influence on the severity markers for 25% of patients.

Conclusion: This work serves as a proof of concept that objective quantitative EEG markers of seizure severity can be employed. These markers can distinguish between seizure types and are therefore sensitive to expected differences in seizure severity. We also provide direct evidence for circadian modulations of seizure severity, as measured by our markers; therefore, our results support past studies hypothesising and hinting at such modulations. Thus, we suggest that our proposed markers could be used to complement existing measures of seizure severity in the future.

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Prognosis of structural acute symptomatic seizures – a prospective observational study

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Purpose: Contrary to current guidelines, acute symptomatic seizures frequently prompt initiation of long-term antiseizure medication treatment. Following data gathered in the 1950s to 1980s, acute symptomatic seizures bear a low risk of subsequent unprovoked seizures (<20% per 10 years). By contrast, in epilepsy, the risk of subsequent unprovoked seizures is >60% per 10 years (Hesdorffer DC et al. Epilepsia 2009; 51(4):671-5). However, until now, studies did not control for the use of antiseizure medication. We hypothesised that after a first acute symptomatic seizure of structural aetiology treated according to current guidelines, the 12-months risk of unprovoked seizure relapse is <25%.

Method: We present a multicentre, prospective, single-arm, open observational study. Subjects aged ≥18 with an acute symptomatic first seizure were included if there was no status epilepticus. Patients are followed up during their intra- and posthospital course for a total of 12 months. Unprovoked seizure relapse is the study’s primary endpoint. The study was prospectively registered in the German Clinical Trials Register (DRKS00017811).

Results: Between September 2019 and July 2021, 10 centres across Germany recruited 115 patients with acute symptomatic seizures of structural aetiology. As of January 2022, 12-month follow-up was completed in 78 participants (68%) while 12 (10%) were lost to follow-up. So far, eight participants (7%) had an unprovoked seizure relapse. The resulting Kaplan-Meier estimator at 12 months is at 10%. While 53% took antiseizure medication for >3 months, ongoing antiseizure medication did not prevent unprovoked seizures. By the time of the ECE in July 2022, follow-up will be completed in the remaining participants.

Conclusion: Our data confirm that even in case of structural aetiology, acute symptomatic seizures are associated with a low risk of subsequent unprovoked seizures. Physicians should refrain from initiating long-term antiseizure treatment after acute symptomatic seizures.
“Benign” EEG for prognostication of favorable outcome after cardiac arrest: a reappraisal

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Purpose: The current role of EEG arrest for prognostication after cardiac is based on the ACNS criteria, as defined by Westhall et al. 2014 ("highly malignant", “malignant”, “benign”), and aims at reliably identifying patients with poor prognosis. Conversely, “benign EEG”, defined by the absence of elements attributed to the other two categories, seems to have limited sensitivity in detecting good prognosis.

We postulated that a less stringent “benign EEG” definition (i.e.: reactive, without epileptiform features other than triphasics; in addition to Westhall’s definition, regardless of voltage and development, discontinuous background is allowed), would improve identification of patients with favorable outcomes.

Method: Analysis of a prospective adult registry (1.2018-9.2021, 383 patients), with predictive performances using 2x2 tables (and binomial 95% CI), and comparisons towards Westhall’s benign classification. Good outcome was defined as CPC 1-2 at 3 months.

Results: The modified “benign EEG” definition lead to identification of a greater number of patients with good outcome. Sensitivity of the new EEG definition occurring at any time within the first 72 hours was 0.94 (95% CI: 0.92-0.97) vs 0.67 (95% CI: 0.60-0.73) for Westhall’s definition (p<0.001). Corresponding positive predictive values (PPV) were 0.53 (95% CI: 0.46-0.59) versus 0.59 (95% CI: 0.51-0.67) for Westhall’s definition (p=0.27). Similar statistics were observed for survivors.

Conclusion: The refined “benign EEG” classification demonstrated a markedly higher sensitivity for favorable outcome and survivors, with minor impacts on PPV. The challenge being to identify these patients efficiently, in order to concentrate resources on them, the present adaptation of the pre-existing criteria of “benign EEG” appears to represent a promising improvement of prognostication in this clinical setting.

Seizure detection using subcutaneous ECG during video-EEG-monitoring and home monitoring; a prospective, proof-of-concept study

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Purpose: Heart rate variability algorithms based on wearable ECG devices have proved to detect not only generalized convulsive seizures, but also focal seizures in patients with ictal autonomic changes. In this proof-of-concept study, we tested whether the ECG-signals from an implantable cardiac monitor (ICM) could be used to detect seizures in two patients with focal epilepsy.

Method: The subcutaneous ICM device (Confirm Rx™, Abbott) was implanted on the first day of the patient’s stay in the epilepsy monitoring unit (EMU). A smartphone app (myMerlin™, Abbott) was installed on the patient’s smartphone. The patients and their families received instructions on how to use the app and to mark an event after experiencing a seizure, which would save the previous 14 minutes and upcoming one minute of ECG.

The patient-tailored seizure detection threshold was set using the first 24-hours of the patients ECG-data obtained from a wearable ECG-patch by using a ECG-based seizure detection algorithm as previous described (Jeppesen J et al. Epilepsia 2019;60:2105-2113).

The patients and their families were asked to record as many seizures as possible during a two-to-four-month home monitoring period and also to record interictal control epochs.

Results: In total, 21 of the 22 seizures recorded with the subcutaneous ICM were detected with the seizure detection algorithm. Six of the seizures were recorded in the EMU (Patient-1: one focal, one focal-to-bilateral-tonic-clonic; Patient-2: four focal), and 16 seizures were recorded in the home monitoring period (Patient-1: four seizures, Patient-2: eleven seizures; all likely focal). No false detections were found in the 44 control epochs.

Conclusion: This proof-of-concept study demonstrates that subcutaneous ICM can be used to detect focal epileptic seizures in a home monitoring setting. Future technology developments allowing long-term continuous real-time data transmission from the implanted ICM-device is needed in order to alert patients about seizures.
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Reduced REM sleep: a potential biomarker for diagnosing epilepsy at epilepsy monitoring units

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Purpose: Establishing the diagnosis of epilepsy can be challenging if interictal epileptic discharges (IEDs) or seizures are undetectable. Many individuals with epilepsy experience sleep disturbances, and a reduced percentage of REM sleep (REM%) has been observed following seizures. We aimed to assess whether REM% differed in individuals with epilepsy compared with individuals with differential diagnoses.

Methods: We performed a retrospective, monocentric, two-armed case-control study with 128 age-matched individuals who underwent ≥72 hours of continuous video-EEG monitoring at the epilepsy monitoring unit (EMU) for evaluation of potential epileptic events. We assessed REM% on the first and the last night of EMU admission. Binary logistic regressions models were used to evaluate the predictive value of REM%.

Results: Upon discharge, 64 individuals were diagnosed with epilepsy, 64 with a differential diagnosis. Mean REM% in the epilepsy group was significantly lower [12.2% (±4.7) vs. 17.2% (±5.2), p<0.001]. We found no significant influence of sex, age, anti-seizure medications, and comedications. A REM%-based and an IED-based regression model were equally effective in predicting the diagnostic group [area under the curve (AUC) 0.797 vs. 0.799]. A model based on IEDs and REM% was superior to the IED-based model alone [AUC 0.897, p<0.001].

Conclusion: Our study shows significantly lower REM% in individuals with epilepsy. REM%-based models show a good predictive performance. REM% assessment could support the diagnostic workup at EMUs when IEDs or seizures are absent and patient history and semiology appear ambiguous. REM% as a biomarker should be evaluated in prospective, multicentric trials.

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Exploratory study of blood biomarkers in patients with post-stroke epilepsy

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Purpose: Stroke is the main etiology of epilepsy in older adults. Blood biomarkers can provide information additional to the clinical risk factors of post-stroke epilepsy. Our aim is to describe new serum biomarkers present at the onset of stroke in patients who develop post-stroke epilepsy and to evaluate their expression at 5-year follow-up.

Methods: Of 51 patients with post-stroke epilepsy (ischemic and hemorrhagic) we selected 15 patients with epilepsy and 15 controls matched for age, sex, type and severity of stroke. We analyzed 480 proteins (Olink®, 5 panels of 96 proteins [inflammation, neurological, cardiovascular I and II, cardioembolic] at baseline (<6 hours from stroke onset) and at 5-year follow-up. Differences in expression in both samples and changes in their behavior over time were evaluated.

Results: Fifteen patients with post-stroke epilepsy (mean age 61.7±10.5; 13.3% female) and 15 controls were included. Nine proteins were down-expressed in the baseline sample (CASP-8, TNSF-14, STAMB, ENRAGE, EDA2R, SIRT2, TGF-alpha, OSM and CLEC1B). The pattern of behavior over time was different for TNFSF-14 (Epilepsy (E): +11.4%, Controls (C): -7.5%), CLEC1B (E: +5.1%, C: -1.8%) and OSM (E: +7.9%, C: -3%). A greater relative increase in the following biomarkers was identified in patients with epilepsy at 5-year follow-up: SRC (E: +2.6%, C: -18.2%) and ST1A1 (E: 16.1%, C: -29.2%).

Conclusion: Patients with post-stroke epilepsy have a different protein expression compared to those without seizures. These results could suggest a dysregulation in protein function, which could also be involved in post-stroke epileptogenesis.
How is (mesial) frontal lobe seizure semiology characterised in post-surgical seizure-free paediatric patients? A retrospective analysis at Great Ormond Street Hospital, London

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Purpose: Seizure semiology is vital in localising the seizure onset zone (SOZ) prior to surgical resection for focal epilepsy, but studies specifically addressing frontal lobe epilepsy (FLE) in children, are scarce. We aimed to identify characteristics of seizure semiology at sub-lobar level in paediatric FLE (pFLE) patients while also assessing the impact of age on semiological features.

Method: We retrospectively identified 43 pFLE patients who were seizure-free after resective surgery at Great Ormond Street Hospital (GOSH) between 2010 and 2020. We analysed pre-operative ictal seizure semiology from video-electroencephalography (vEEG) recordings and stratified them by resection region (mesial or lateral frontal lobe), and age at surgery.

Results: pFLE is characterised by short, frequent, complex seizures, similar to adult cohorts. Children with mesial versus lateral FLE exhibit more contralateral head-deviation (33.3% vs 0.0%; p=0.009; forced contralateral head-deviation: 26.7% vs 0.0%; p=0.03), ictal body-turning (IBT: 53.3% vs 15.0%; p=0.03; ipsilateral IBT: 46.7% vs 5.0%; p=0.01), and complex motor signs (80.0% vs 45.0%; p=0.046). Both age groups (under 7 years old versus aged 7 and older) exhibited hyperkinetic features (20.0% vs 40.0%) in contrast with previous reports. Less contralateral IBT, distal stereotypies and complex behavioural seizure components were observed in younger versus older children (contralateral IBT: 0.0% vs 20.0%, p=0.046; distal stereotypies: 36.0% vs 73.3%, p=0.048; complex behaviour: 40.0% vs 80.0%, p=0.02).

Conclusion: This study is the largest, most detailed semiological analysis of children with focal epilepsy of confirmed frontal lobe origin. Children with pFLE demonstrate semiological features which may help to differentiate between mesial and lateral SOZs. While age-dependent differences in semiology exist, typical frontal lobe features (e.g. hyperkinetic seizures) are seen even in the very young. Greater understanding of paediatric seizure semiology might lead to increased accuracy in identifying the SOZ and earlier pre-surgical evaluation, which is associated with better outcomes.
Imaging the cytoarchitectural changes within focal cortical dysplasias using diffusion tensor imaging

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Purpose: Diffusion tensor imaging (DTI) has the potential to lend insight into the cytoarchitectural changes associated with focal cortical dysplasia (FCD), the predominant aetiology of paediatric structural epilepsy. However, DTI changes in FCD have remained largely unexplored in this population, which could profit the most from novel biomarkers. We investigated if DTI indices differed between FCD and contralateral brain parenchyma (CBP) and if alterations in specific clinical features affected DTI values.

Methods: In this single-centre retrospective, cross-sectional study, we considered children and adolescents with focal structural epilepsy associated with FCD who underwent brain MRI, including DTI sequences, in our institution. FCDs were manually segmented on high-resolution 3D T1-weighted MRI, and the DTI parameters of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity, and radial diffusivity were calculated in both FCD and CBP, after normalizing the DTI to the anatomical images. DTI indices facilitating an optimal differentiation between FCD and CBP were further analysed to determine if clinical features affected DTI values.

Results: 32 patients (20 male; mean age at MRI 6.0 ± 4.7 years) were enrolled in this study: FCD was histologically confirmed in 15 of 32 cases. FA values were lower in FCD compared to CBP (p=0.028), whereas MD values were higher in FCD than in CBP (p=0.044). In histologically confirmed FCD, the difference in FA values between FCD and CBP was higher for FCD type IIb than for FCD type I (p=0.033), and for patients with a positive vs. negative history of status epilepticus (p=0.015), while none of the clinical features influenced the difference in MD values.

Conclusion: FA values can discriminate FCD from CBP and distinguish between FCD subtypes, whereas status epilepticus can lead to an increase in FA values. DTI may prove a powerful tool for FCD identification and differentiation, thus improving outcomes in the paediatric population.

A neverending challenge: epilepsy secondary to MECP2 mutation

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Purpose: Epilepsy is common in Rett syndrome (RTT), an X-linked dominant disorder caused by mutations in the MECP2 gene, but its characteristics and management of epilepsy has not been sufficiently explored.

Method: Retrospective study of 43 girls <18 years of age with pathogenic mutation in MECP2. Patients were categorized according to classic (RTTC), atypical Rett syndrome (RTTA) and patients with mutation without clinical syndrome.

Results: 26 patients had RTTC: 18 (70%) had epilepsy (mean onset 7 years [2-13]). Seizures were generalized tonic-clonic (TCGS) or focal motor tonic (FMT), being reflex in 8 (30%) (triggers: 4 hyperventilation, 1 photosensitive and 1 laughter). The initial EEG had centrotemporal spikes (CTS) and only one patient had epileptic encephalopathy pattern (EE). In 12 (66%) epilepsy was refractory with a mean AEDs number of 3.2. The most effective drug was topiramate (12/12), especially in reflex seizures triggered by hyperventilation, followed by valproic acid (VPA) (13/18). Levetiracetam was ineffective (0/11).

17 patients presented RTTA: 8 (47%) had epilepsy [mean onset 3.5 years (2-6)], seizures were similar semiology, without reflex seizures. The EEG had CTS in 2, and 4 patients had a EE pattern. In 6 (75%) the epilepsy was refractory with a mean AEDs number of 4. The most effective drug was topiramate (4/4) and VPA (5/6).

3 patients without RTT clinical, had epilepsy [mean onset 6.3 years (4-11 years)]. All presented a multifocal EEG with evolution to Lennox-Gastaut syndrome. The mean AEDs number was 5. VPA was effective in 2/3 and topiramate in 1/3.

Epilepsy characteristics had not correlated with severity scales. Genotype did not predict the frequency and type of epilepsy.

Conclusion: Refractory epilepsy is common in RTT. In the classic phenotypes, reflex seizures are more frequent, while in the RTTA or mutation in MECP2 without RTT clinical evolution to epileptic encephalopathy is more frequent.
The ENVISION Study, an international, prospective natural history study in young children with SCN1A+ Dravet syndrome

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Purpose: Dravet Syndrome (DS) is the prototypic developmental and epileptic encephalopathy characterized by drug-resistant seizures and developmental impairment. There are limited contemporary, prospective long-term data describing the full range of phenotypic features and evolution, and the impact of DS in young children. ENVISION is a comprehensive observational study aimed at prospectively evaluating the course and impact of disease in young children living with SCN1A+ DS and families. Data collected during 1 ½ year of study will be presented.

Methods: Ongoing international, multicenter, longitudinal, prospective study of children with DS with a confirmed SCN1A pathogenic or likely pathogenic variant, aged 6 months to 5 years at study entry. Participants are assessed remotely every 3 months (6 in-person) for 24 months to evaluate the longitudinal progression of various endpoints using an electronic seizure diary and validated tools, including Bayley-III, Vineland-III, and PedsQL.

Results: As of 5Nov2021, 45 participants have been enrolled (mean age 31 months). Approximately 40% of participants were aged ≤2 years at enrollment (19/45) and over 70% have truncating variants (32/45). Despite multiple antiseizure medications (median 3; range 1–6), median monthly countable seizure frequency (MCSF) increases with age. High MCSF heterogeneity was observed (range 0–2647 seizures per 28 days at 3-month visit). Regardless of variant type, participants showed substantially decreased neurocognitive abilities by age 3 years; children aged 4–5 years show skills comparable to neurotypical children at age 2 years. Gross/fine motor skills are impaired in children with DS younger than 3 years of age. Quality of life is impaired and worsens with age, functional abilities are affected as early as 2 years of age.

Conclusions: Initial ENVISION data demonstrate the trajectory and timing by which children with DS deviate from neurotypical peers and highlight the early therapeutic window for disease-modifying therapies to provide maximum benefit.
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**Donepezil as precision therapy for gain-of-function variants in KCNQ2/KCNQ3 encephalopathy**

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**Purpose:** The KCNQ2/KCNQ3 genes encode for the voltage-gated-K-channel underlying the M-current, regulating neuronal excitability. Loss-of-function variants cause neonatal epilepsy, treatable with M-current openers. Gain-of-function variants present with later onset epilepsy and developmental disability, and could be amenable to M-current blockers, but such therapies are not available. In this translational project we research whether donepezil, a cholinergic drug used in Alzheimer could suppress the M-currents in-vitro and improve symptoms in patients with gain-of-function variants.

**Method:**

1/ **Laboratory methods:** The effect of 1 µM donepezil on the amplitude of M-current was measured separately in excitatory and inhibitory neurons of primary cultured hippocampal cells [14–16 d in-vitro]. To identify GABAergic neurons, we infected hippocampal cultures with a recombinant virus derived from an AAV-viral vector driving the expression of the fluorescent protein mCherry under the control of the specific GABAergic hDlx promoter. The M-current was measured by standard deactivation protocol (holding at 0 mV and deactivation at −60 mV) in the whole-cell configuration of the patch-clamp technique. The M-current was determined by the amplitude of the tail.

2/ **Exploratory study:** Three patients bearing gain-of-function variants- KCNQ2(p. Arg144Gly), KCNQ3(p.Arg227Gln, p.Arg230Cys) will be administered donepezil 5mg/d for 6 months. Outcome measures will be seizure frequency, epileptiform activity on sleep-EEG and neuropsychological tests (ABAS-II, CDI, CARS-2).

**Results:**

1/ Application of 1 µM donepezil produced within 3-5 min a significant inhibition of 67% of the M-current amplitude (2.4±0.46 vs.0.89±0.15pA/pF, p<0.01). In inhibitory neurons, application of 1 µM donepezil produced a lesser inhibition of 59% of the M-current amplitude (1.39±0.43 vs. 0.57±0.21, p=0.053), which did not reach statistical significance.

2/ We expect donepezil to improve cognitive outcome measures by 20% and reduce seizure frequency by 50%.

**Conclusion:** Donepezil would be a repurposed drug, used as precision treatment for gain-of-function variants in KCNQ2/KCNQ3 encephalopathy.

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**Neonatal seizures: use of the last ILAE Classification in a retrospective observational cohort study**

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**Purpose:** Neonatal seizures are the most common neurological emergency in newborns. The majority of seizures occur in response to an acute brain insult. A smaller number of cases are due to non-acute genetic or malformative etiologies. The aim of this study was to classify our patients’ seizures according to the last ILAE classification.

**Methods:** This was a retrospective observational cohort study of all the neonatal cases with video EEG-confirmed seizures, recorded between January 2015 and August 2021 at Bambino Gesù Children's Hospital. During this period, 886 newborns (494M) required a neurological evaluation in the Neonatal Intensive Care Unit; among them, 11.6% (103, 60M) presented seizures. Perinatal history, primary diagnosis, age at seizures onset, semiology of seizures and EEG features were analysed, applying the last ILAE classification for neonatal seizures.

**Results:** A total of 38 (20M) cases with video-EEG recorded seizures were included. Median age at onset was 7.8 days (range: 1-28 days ± 9.3 DS). Median gestational age was 38.6 weeks (range: 33.5-41.2 weeks ± 1.8 DS). The most frequent etiologies were HIE (17), stroke (7) and DEE (4). The duration of EEG recordings ranged from 30 minutes to 48 hours. We recorded 491 single seizures and 6 Status Epilepticus. 217 seizures were electrographic-only, due to HIE in 14 patients. 22 patients presented electroclinical seizures and the most frequent type (11/22) was clonic, due to acute etiologies. Tonic seizures were mainly observed in patients with DEE.

**Conclusions:** The new ILAE classification appears to be comprehensive. Using seizures type and descriptors, we were able to include all our patients in a specific category.
Altered correlation of simultaneously recorded EEG-fMRI connectomes in temporal lobe epilepsy

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**Purpose:** Whole-brain functional networks/connectomes have been characterized on different temporal and spatial scales in humans using EEG and fMRI but the precise relationship between those results is unclear. Here, we aim to characterize the spatial correlation between EEG and fMRI connectomes in left and right temporal lobe epilepsy (r/ITLE) using simultaneous EEG-fMRI recordings.

**Method:** From two independent centers, we acquired resting-state concurrent EEG-fMRI of 35 healthy controls (21 Geneva, 14 Marseille) and 34 TLE patients (23 Geneva, 11 Marseille). The data – averaged fMRI activity and EEG source imaging - was projected onto the same brain atlas. For each subject, connectomes based on fMRI (using Pearson correlation) and EEG (using imaginary coherence) were calculated. Correlations between the group-averaged EEG and fMRI connectomes were statistically compared by permuting the group labels.

**Results:** For all groups average EEG and fMRI connectomes were correlated ($r \approx 0.3-0.4$). For both imaging centers, correlation between EEG and fMRI connectivity was significantly increased in rTLE ($p < 0.05$ corrected) when compared to controls (all bands, except gamma). In contrast, ITLE patients showed a significant decrease for the correlation between EEG-beta and fMRI connectivity compared to controls ($p < 0.05$ corrected). While changes in rTLE patients were linked to a global increase of spatial correlation, the changes in ITLE were spatially localized in the default mode network and the limbic network.

**Conclusion:** EEG and fMRI connectomes are correlated for both healthy subjects and patients. The increased correlation of EEG-fMRI in rTLE patients indicates a synchronization of brain activity across all measured timescales suggesting a reduced functional repertoire in rTLE patients but not ITLE patients. This is in line with previous work showing a global bilateral reorganization of functional and structural networks in rTLE as opposed to more local changes in ITLE.

MELD project: MRI automated detection and atlasing of lesions in focal cortical dysplasia

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**Introduction:** Drug-resistant focal epilepsy is often caused by focal cortical dysplasias (FCDs) which are notoriously difficult to visually identify on structural MRI but are amenable to surgical resection. We aimed to develop an open-source, interpretable, surface-based machine-learning algorithm to automatically detect FCDs on heterogeneous structural MRI data from epilepsy surgery centres worldwide.

**Methods:** The MELD Project collated and harmonised a retrospective MRI cohort of 1015 participants, 618 patients with focal FCD-related epilepsy and 397 controls, from 22 epilepsy centres worldwide. We trained a neural network to detect FCDs based on multiple surface-based features. The network was trained and cross-validated on 50% of the cohort and tested on the remaining 50%. We used integrated gradient saliencies to interrogate network performance.

**Results:** For all groups average EEG and fMRI connectomes were correlated ($r \approx 0.3-0.4$). For both imaging centers, correlation between EEG and fMRI connectivity was significantly increased in rTLE ($p < 0.05$ corrected) when compared to controls (all bands, except gamma). In contrast, ITLE patients showed a significant decrease for the correlation between EEG-beta and fMRI connectivity compared to controls ($p < 0.05$ corrected). While changes in rTLE patients were linked to a global increase of spatial correlation, the changes in ITLE were spatially localized in the default mode network and the limbic network.

**Conclusion:** EEG and fMRI connectomes are correlated for both healthy subjects and patients. The increased correlation of EEG-fMRI in rTLE patients indicates a synchronization of brain activity across all measured timescales suggesting a reduced functional repertoire in rTLE patients but not ITLE patients. This is in line with previous work showing a global bilateral reorganization of functional and structural networks in rTLE as opposed to more local changes in ITLE.
Focal “scalp-invisible” epileptic activity is associated with increased large-scale brain network efficiency

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Purpose: In focal epilepsy, the activity of physiological brain networks is disrupted also during periods without any epileptic discharges visible in scalp EEG. Simultaneous recordings showed that only a minority of epileptic spikes detected by intracranial EEG (iEEG) also appear on the scalp. We aimed at comparing network features in epochs of scalp-hidden spikes (iEEG-IED periods) and epochs free of spikes on both scalp EEG and iEEG (rest periods).

Methods: Simultaneous hd-EEG/iEEG was recorded in 9 patients with pharmacoresistant focal epilepsy. We identified 2 sets of epochs in each patient: i) intracranial hippocampal IEDs (iEEG-IED periods) not visible on the scalp and ii) epochs without any epileptic activity in both hd-EEG and iEEG (rest period). The activity of 72 brain regions was estimated using individual head models and distributed inverse solution. We first calculated the event-related spectral perturbation (ERSP) in the hippocampus. Then we computed the connectivity between these 72 brain regions and calculate two measures of network integration and segregation. We statistically compared these measures in the two types of epochs.

Results: The ERSP showed an increase in power from delta to alpha during the iEEG-IED compared to the rest period (p<0.05, FDR corrected). Both the integration and segregation increased during iEEG-IED periods compared to rest periods in broad band and in theta band (p<0.05, FDR corrected).

Conclusion: Even in absence of visible epileptic activity, we first showed that some information of the hippocampal IED reaches the scalp-electrodes and second that changes in the network due to hidden pathological events can be measured with non-invasive means. Moreover, brain activity of patients with epilepsy seems to be differently altered during rest and iEEG-IED periods, arguing in favor of pathological networks during underlying epileptic activity.

7T metabolic MRI in focal epilepsy

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Purpose: To combine different (metabolic) magnetic resonance imaging (MRI) sequences at 7 Tesla to characterize focal epileptogenic lesions, and uncover potential metabolic markers that could help identifying the culprit lesion in MRI-negative epilepsy patients.

Methods: Five patients (aged 23-48 years; three females) and five healthy volunteers (aged 24-27 years; two females) were included. All subjects underwent one (metabolic) 7 Tesla MRI examination including quantitative susceptibility mapping (QSM) and proton (1H) magnetic resonance spectroscopy (MRS). The field-of-view in healthy volunteers was matched with the lesion location in the patients. All patients were diagnosed with hippocampal sclerosis (HS) or focal cortical dysplasia (FCD) and were scheduled for surgical treatment the day after their (metabolic) 7 Tesla MRI examination. Final diagnosis was based on histopathology. QSM images were analyzed qualitatively for differences in iron deposition.

Results: Using QSM, we observed increased iron deposition in the affected hippocampus of two HS patients that was not found in the contralateral hippocampus, neither in a suspected HS patient with no abnormal tissue, nor in matched healthy volunteers. No increased iron deposition was found in patients with FCD or matched healthy volunteers. No significantly different metabolite ratios between patients and healthy volunteers using 1H MRS were found yet.

Conclusion: These preliminary results support previous findings of increased iron deposition using susceptibility-weighted imaging and histopathology in mesial temporal lobe epilepsy (Zimmer TS et al. Neuropathol Appl Neurobiol. 2020;46:546-563; Zhang Z et al. BMC Neurosci. 2014;15:117). This is a first step towards a combined metabolic MRI profile of focal epilepsy at 7 Tesla. Ongoing patient inclusion will increase our sample size, allowing for more robust statistical analyses of our QSM and MRS data.
Emotion perception and recognition in juvenile myoclonic epilepsy

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Purpose: Juvenile myoclonic epilepsy (JME) is the most common age-related idiopathic epilepsy, with an elevated risk of psychiatric disorders. Imaging studies reveal emotional and behavioral problems to be associated with subtle structural and functional alterations mainly in frontal cortex and thalamus. Understanding of pathophysiological mechanisms in emotion perception and recognition in JME, might enable the development of psychological and pharmacological interventional strategies. In this study, we aimed to assess emotion perception and recognition in patients with JME.

Method: We recruited 65 patients (JMEs; 37 female) and 68 controls (HCs; 38 female). All participants underwent 1. The Structured Clinical Interviews for DSM-IV Axis I and Axis II; 2. A Neuropsychological test battery; 3. An emotion recognition test battery (NEmo); and 4. An emotion perception fMRI-paradigm, in which participants passively watched dynamic fearful faces.

Results: Axis I and/or Axis II disorders were diagnosed in 63% of JMEs and 21% of HCs. JMEs performed worse in psychomotor speed, tonic alertness, divided attention, mental flexibility, and inhibition of automated reactions. Emotion recognition (NEmo) was lower in all emotion recognition tasks in total (all emotions), as well as only for the emotion fear. Neuroimaging revealed decreased amygdala activation in JMEs. Duration of epilepsy correlated negative with the NEmo-subtest of parallel prosodic and facial emotion recognition (all emotion and fear), and the verbal learning score. No differences were found when controlling for psychiatric disorders, type of seizure (GCTS/other/none), as well as psychomotor speed.

Conclusion: JME is associated with a decreased bilateral amygdala activation in emotion perception. Our results point to an affective phenotype that is accompanied by a dysexecutive syndrome. Decreased amygdala activity might contribute to aberrant fronto-limbic connections and by that might increase the risk of altered emotion recognition and psychiatric comorbidities.
Disorganization of language and working memory systems in frontal versus temporal lobe epilepsy

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Purpose: Cognitive impairment detrimentally affects both people with frontal lobe epilepsy (FLE) and temporal lobe epilepsy (TLE). While the underlying neural correlates have been extensively investigated in TLE, functional imaging studies in FLE are scarce. Here, we investigated neural processes accounting for cognitive dysfunction in FLE, and directly compared FLE and TLE patients to establish commonalities and differences.

Method: We investigated 172 adults (56 FLE, 64 TLE, 52 controls) using neuropsychological tests and four fMRI tasks probing expressive language (verbal fluency, verb generation) and working memory (verbal and visuo-spatial). Patient groups were comparable in age of epilepsy onset, disease duration, and antiseizure medication load. We mapped task-related brain activation and deactivation using a novel multiscale approach, and tracked reorganization in FLE and TLE. Our analyses complemented voxel-based maps with profiling of task effects across established motifs of functional brain organization: (i) canonical resting-state functional networks, and (ii) the principal functional connectivity gradient, that encodes a continuous transition from lower-level (sensory) to higher-order (transmodal) brain areas.

Results: We find that cognitive impairment in FLE is accompanied by reduced activation across frontoparietal attentional and executive networks, and reduced default-mode network deactivation, indicating large-scale disorganization of task-related recruitment, particularly during working memory. Patterns of dysfunction in FLE and TLE are broadly similar, but some traits are syndrome-specific: impaired default-mode deactivation is more evident in FLE, while impaired recruitment of posterior language areas is more evident in TLE. More severe epilepsy relates to more marked cognitive network disorganization both in FLE and TLE.

Conclusions: Our study elucidates neural processes underlying cognitive impairment in the most common focal epilepsies, identifies frontoparietal executive alterations as a shared biological signature, irrespective of seizure focus localization, and shows that temporal lobe language alterations are TLE-specific. The highlighted systems-level behavior may be amenable to future remediation strategies, including neurostimulation.
D-galactose supplementation for the treatment of patients with mild malformation of cortical development with oligodendroglial hyperplasia in epilepsy (MOGHE): an interim analysis of a proof-of-concept trial

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Purpose: MOGHE is a new entity frequently associated with refractory epilepsy and neurodevelopmental disorders. Recently, it has been associated to SLC35A2 (Solute Carrier Family 35 Member A2) brain mosaic pathogenic variants. In addition, patients with germline SLC35A2 pathogenic variants improve with galactose supplementation. Therefore, the investigators aim to elucidate whether d-galactose as an add-on treatment might improve epilepsy and neurodevelopmental outcomes in patients with MOGHE (clinicaltrials.gov identifier: NCT04833322).

Method: Patients with electroclinical and histopathological features of MOGHE with at least two of the following inclusion criteria (uncontrolled seizures, frequent epileptiform activity at EEG, developmental comorbidity) were included. Main outcomes pre-treatment and 6 months post-treatment were: clinical global impression, seizure frequency, quantification of epileptiform activity at 24h video-EEG, neuropsychological (BRIEF-2, CPT-II, SNAP-IV, WPPSI) assessment. D-galactose was supplemented using validated protocols for patients with SLC35A2 germline mutations, once per day, up to 1.5g/kg per day (Witters P et al, Genet Med, 2020 22(6):1102-1107).

Results: Nine patients were included from January 2021 to January 2022, with epilepsy surgeries performed between 2008 and 2021. Age range was between 6 and 29 years; two females; eight out of nine with frontal lobe origin. Four patients had uncontrolled seizures, eight had cognitive impairment, all presented frequent epileptiform activity at EEG. Three patients reported mild transient digestive symptoms. No other relevant adverse events were found. Four patients had completed the follow-up at the time of this interim analysis: one out of two patients with uncontrolled epilepsy had >50% improvement in seizure frequency. Three out of four patients presented improvements in neuropsychological assessments. There were no relevant changes in EEG quantification.

Conclusion: D-galactose supplementation might be a safe precision treatment for patients with MOGHE. The recruitment of this study is still open and more data regarding follow-up efficacy outcomes is warranted.
Perampanel in rare genetic epilepsies - is there a targeted effect?

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**Purpose:** Perampanel, an antiseizure drug with AMPA receptor antagonist activity might have targeted effect in genetic epilepsies with overactivated glutamate receptors. Special interest hold epilepsies with loss of GABA inhibition (e.g. SCN1a), overactivity of excitatory neurons (e.g. SCN2a, SCN8a, KCNQ2), variants in glutamate receptors (e.g. GRIN2a). Our aim is to collect data on genetic epilepsies treated with perampanel in order to detect subgroups with high efficacy of treatment.

**Method:** This is a multicenter project based on the framework of NETRE (Network for Therapy in Rare Epilepsies), a web of pediatric neurologists treating rare epilepsies. Retrospective data from patients with genetic etiology treated at least 3 months with perampanel was collected. Outcome measures were responder rate (50% seizure reduction), and percentage of seizure reduction. Subgroups of etiologies with high efficacy were identified.

**Results:** 125 patients, with 73 different etiologies, aged 1-57 years (mean 12.09±9.45) were enrolled. The mean dosage was 6.47±2.45 mg, and period of treatment was 1.96±1.77 years (3 months-8 years). 54 patients (43.2%) were treated for over 2 years. 88 patients (70.4%) were responders, and 83 (66.4%) choose to continue therapy. The mean reduction in seizure frequency was 55.44%. 53 patients (42.3%) had over 75% reduction in seizure frequency, including 31 (24.8%) with over 90% reduction in seizure burden. The following etiologies showed high efficacy of treatment: SCN1a, GNAO1, PIGA, PCDH19, SYNGAP1, TSC2, POLG1, POLG2. 85% of patients with SCN1a were responders, 37.5% of them had over 90% reduction in seizures. Other etiologies remarkable for over 90% reduction in seizures were GNAO1 and PIGA. 14 patients had ESES, but only in 3 perampanel reduced epileptiform activity.

**Conclusions:** Perampanel showed a high efficacy in patients with rare genetic epilepsies. Etiologies like SCN1a, GNAO1, PIGA, SYNGAP1 showed an especial efficacy, suggesting a targeted effect related to glutamate transmission.
Treatment of status epilepticus in poststroke epilepsy with last generation anti-seizure medication

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Purpose: Status epilepticus in poststroke epilepsy (PSE) is challenging condition due to vascular comorbidities and advanced age of patients. The evidence on the treatment of status epilepticus in PSE is generally limited and not available for new generation anti-seizure medications (ASMs).

Methods: Data on the effectiveness and safety of new generation ASM in status epilepticus in PSE was gathered from two German stroke registries and Mainz Epilepsy Registry. The following ASMs were included: brivaracetam (SV2A selective agonist), perampanel (AMPA antagonist), lacosamide and eslicarbazepine (both slow sodium channel inactivation). Logistic regression was performed to identify predictors of successful treatment of status epilepticus in PSE.

Results: Of 101 patients with status epilepticus in ischemic PSE, 33 (32.7%) were treated with lacosamide, 21 (20.8%) with perampanel, 24 (23.8%) with brivaracetam and 23 (22.8%) with eslicarbazepine. The mean age was 70.78 (+/-8.4) years. On average, 2 other ASMs were administrated prior to start the one of the above mentioned ASMs. Lacosamide was titrated up to 400 mg/d, brivaracetam to 200 mg/d, perampanel to 16 mg/d and eslicarbazepine to 1600mg/d. The effectiveness was assessed based on seizure freedom within 48 hours since the start of respective ASM. This was achieved in 37.5% with brivaracetam, 38.1% with perampanel, 66.7% with lacosamide and 65.2% with eslicarbazepine (p<0.05). Independent predictors of interruption of status epilepticus in PSE were an earlier start of new generation ASM, lower number of previous ASMs and absence of smoking or atrial fibrillation.

Conclusion: Based on this data, it can be assumed that the use of lacosamide and eslicarbazepine is associated with a better efficacy in the treatment of status epilepticus in PSE. The slow inactivation of sodium channels as the mechanism of action of lacosamide and eslicarbazepine may have beneficial effects in the treatment of this etiological entity of status epilepticus.

Effect of add-on cannabidiol on seizure frequency and seizure-free intervals in patients with seizures associated with tuberous sclerosis complex: phase 3 trial GWPCARE6 post-hoc analysis

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Purpose: This post-hoc analysis of a randomised, placebo-controlled phase 3 trial (GWPCARE6; NCT02544763) evaluated seizure frequency reduction to determine the proportion of patients with tuberous sclerosis complex (TSC), treated with cannabidiol (CBD) or placebo, who reached all continuous responder rate thresholds and the longest seizure-free intervals.

Methods: Patients received plant-derived highly purified CBD medicine (Epidyolex® [GW Research Ltd]; 100 mg/mL oral solution) at 25 mg/kg/day (CBD25) or 50 mg/kg/day, or matched placebo for 16 weeks. Efficacy of CBD25 (n=75) vs placebo (n=76) was evaluated by percent reduction from baseline in TSC-associated seizure frequency and longest seizure-free intervals.

Results: In the 4-week baseline period, median (Q1, Q3) TSC-associated seizure frequency was 56 (21, 101) for CBD25, 54 (26, 102) for placebo; mean (standard deviation [SD]) longest seizure-free interval was 3 (3) days for CBD25, 2 (2) days for placebo. CBD produced significantly greater reduction in TSC-associated seizures vs placebo (treatment ratio [95% CI], 0.699 [0.567–0.861]; P=0.0009). Response rates for ≥25%, ≥50%, and ≥75% reduction: 68%, 44%, and 19% for CBD25; 43%, 22%, and 0% for placebo. Mean (SD) longest seizure-free intervals: 11 (17) days for CBD25 and 6 (6) days for placebo. CBD25 vs placebo 7-, 14-, 21-, and 28-day seizure-free intervals: 45% vs 33%, 24% vs 14%, 12% vs 0%, and 8% vs 0%. AE incidence: 93% for CBD25 and 95% for placebo; 8 patients (11%) on CBD25 and 2 (3%) on placebo discontinued treatment because of an AE. Most common AEs: diarrhoea and decreased appetite, occurring more frequently with CBD than placebo. ALT/AST elevations (>3× ULN) occurred in 9 (12%) patients on CBD25 and none on placebo; 78% were on concomitant valproate.

Conclusion: CBD was superior to placebo, reducing seizures and producing longer seizure-free intervals in patients with TSC-associated seizures.

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Long-term efficacy and safety of perampanel monotherapy in patients with newly diagnosed/currently untreated recurrent focal-onset seizures: FREEDOM Study 342 Extension Phase

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Purpose: FREEDOM (NCT03201900) showed that perampanel 4–8 mg/day monotherapy was efficacious and generally well tolerated in patients aged ≥12 years from Japan/Korea with newly diagnosed/currently untreated recurrent focal-onset seizures (FOS), with/without focal to bilateral tonic-clonic seizures. We report long-term (52 weeks: up to a maximum of 24 months) efficacy and safety from the Extension Phase.

Method: During the Core Study, patients received perampanel 4 mg/day (4-week Pretreatment [baseline]; 32-week Treatment [6-week Titration; 26-week Maintenance] with the possibility to up-titrate to 8 mg/day). Patients could enter an Extension Phase for an additional 26 weeks (52 weeks). 52-week and 24-month seizure-freedom rates and treatment-emergent adverse events (TEAEs) (Core/Extension) were assessed.

Results: Overall, 89 patients received ≥1 perampanel dose (Safety Analysis Set). Of these, 73 patients entered the 4-mg/day Maintenance Period (modified Intent-to-Treat Analysis Set); 21 patients entered the 8-mg/day Treatment Phase. Overall, 46/67 (68.7%) eligible patients entered the Extension (39 who completed the 4- or 8-mg/day Treatment Phases [4-mg/day, n=32; 8-mg/day, n=7] and seven who discontinued the 8-mg/day Treatment Phase); 38 patients completed the Extension and eight discontinued, most commonly due to withdrawal of consent (n=3 [6.5%]). Overall, 24/32 (75.0%) and 20/32 (62.5%) patients who entered the Extension from the 4-mg/day Treatment Phase and seizure free had sustained seizure freedom for 52 weeks and 24 months, respectively; corresponding values from those who entered from the 4and/or 8-mg/day Treatment Phase were 31/39 (79.5%) and 22/39 (56.4%), respectively. TEAEs occurred in 74/69 (83.1%) patients, most commonly dizziness (38.2%).

Conclusion: Final results of FREEDOM suggest seizure freedom can be sustained during long-term (up to 24 months) treatment with perampanel monotherapy at doses as low as 4 mg/day in patients with newly diagnosed/currently untreated recurrent FOS. Perampanel was generally well tolerated and no new TEAEs were reported.

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Stiripentol efficacy and tolerability for drug-resistant epilepsy treatment in tuberous sclerosis complex

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Purpose: This study aims to assess the efficacy and tolerability of stiripentol (STP) in tuberous sclerosis complex (TSC) patients with drug-resistant epilepsy.

Method: A retrospective review of all TSC patients at Cincinnati Children's Hospital from 2011 until 2021 was performed to identify patients treated with STP. Seizure frequency was assessed 1 month before (considered as baseline) and 1, 3, 6, and 12 months after STP initiation.

Results: Of the 1492 TSC patients, 13 (10 males and 3 females) received STP. The age range was 3.8 to 40 years (median, 25th, 75th percentile = 15.2 years, 6.7, 22.0). STP was initiated a median of 13.5 years (25th and 75th percentile = 5.0 & 20.3) after seizure onset. The median length of treatment was 12.8 months and a median STP dose was 21.1 mg/kg/day (25th and 75th percentiles = 12.8 and 34.1) and 750 mg/day (range 500-2250). The number of patients with >50% seizure reduction was 6/13 (46.2%), 4/13 (30.8%), 8/11 (72.7%), and 6/8 (75.0%) at 1, 3, 6, and 12 months. 11/13 (84.6%) patients experienced seizure reduction. Importantly, 6 patients (46.2%) had persistent seizure freedom from 1 through 12 months, with the mean ±SD percentage of reduction at 1, 3, 6, and 12 months of 68.1% (±22.0), 71.3% (±23.2), 75.7% (±23.5), and 75.7% (±23.5), respectively. 2/13 (15.4%) reported worsening in seizure frequency with the treatment. 11/13 (84.6%) patients reported side effects, with aggression in 8 patients (61.5%) and resulting in 3 patients discontinuing STP. Poor sleep, drowsiness, tremor, appetite change, and flat affect were reported.

Conclusion: Most TSC patients with drug-resistant epilepsy who were treated with STP experienced seizure reduction, with almost half having a persistent seizure reduction. This suggests that STP could be an efficacious and tolerable treatment option for this population.
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Ictal semiology of epileptic seizures with insular and temporal genesis

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**Purpose:** Epileptic seizures with insular genesis are often difficult to distinguish from those originating in the temporal lobe due to their variable semiology and complex electrophysiology. The aim of this work is to analyze differentiating characteristics in seizures with insular and temporal origin.

**Method:** Retrospective analysis of the semiology in 46 patients with a diagnosis of insular epilepsy (IE) in comparison to age-matched controls with mesial temporal lobe epilepsy (MTE).

**Results:** The most prominent ictal features in IE were focal motor phenomena in 80.4% of the patients. Somatosensory sensations, version, tonic and clonic features, when present, were more frequent contralateral to the epileptogenic region in MTE patients, while they occurred about equally often ipsilateral and contralateral to the epileptogenic region in IE patients. Ipsilateral manual automatisms were significantly more frequent in MTE than in IE (p=0.010). A multivariate analysis using 5 semiologic features correctly identified IE in 78.3% and MTE in 84.8% (Chi-square=53.79, p<0.0001). A subanalysis using only the earliest ictal signs for comparing patients with purely insular lesions with MTE patients showed that somatosensory sensations are significantly more frequent in insular epilepsy (p=0.010), while automatisms were significantly more frequent in MTE patients (p=0.006). Two major symptom clusters in IE patients were identified: Cluster 1 comprised subjective feelings including fear, olfactory, gustatory, auditory, déjà-vu, somatosensory, cephalic or epigastric sensations, ictal speech and hyperkinetic features whereas cluster 2 comprised behavior arrest, automatisms, aphasias, autonomic and focal motor features.

**Conclusion:** The analysis of ictal semiology allows to differentiate IE and MTE in a large fraction of patients. The detected differentiating features are relevant for the correct localization of seizure generators in the framework of presurgical evaluation and epilepsy surgery.

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Is drug resistant temporal lobe epilepsy in fact a neurodegenerative disorder?

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**Purpose:** Temporal lobe epilepsy (TLE) is the most prevalent form of drug-resistant epilepsy with hippocampal sclerosis representing the most common primary pathology. Cognitive decline along with mood disorders have been well-described co-morbidity of TLE patients. Recently, there has been a growing interest in exploring the contribution of the neurodegeneration pathways in epilepsy in search of possible therapeutic targets. Amyloid-β (Aβ) and tau protein are the most explored proteins associated with neurodegeneration processes.

**Method:** Hippocampal and cortical tissue samples from anteromedial temporal lobe resections of 93 patients suffering from drug-resistant temporal lobe epilepsy with hippocampal sclerosis treated in Brno Epilepsy Center (age range – 18 to 64) were immunohistochemically analyzed for presence of Aβ, phosphorylated tau protein and cerebral amyloid angiopathy (CAA). Tau pathology was quantified using a modified tau score created specifically for analysis of temporal lobectomy tissue and the Braak staging, which was limited without extra-temporal brain areas available.

**Results:** 88 out of 93 specimens (95%) showed hyperphosphorylated tau brain pathology. Comparing patients aged 11-30 years at the time of the surgery (25 cases) with age-matched population controls from post-mortem series of 85 patients in the large population study of professor Braak was found a significantly higher burden of tau pathology (p < 0.001) within Braak stages III-IV. Aβ pathology was found in 21 out of 93 specimens (23%). In 17 (18%) was found CAA.

**Conclusion:** Our study shows the greater hyperphosphorylated tau protein burden in the tissue resected from patients with drug-resistant TLE in comparison to the normal population. Cerebral amyloid angiopathy was described in the resected tissue from the patients with epilepsy for the first time. These findings point to the substantial role of the neurodegeneration pathways in drug-resistant epilepsy. Further studies comprising an autopsy control group together with more neurodegeneration proteins (such as alpha-synuclein) are needed.
Risk of epilepsy after a single unprovoked seizure in individuals after traumatic brain injury

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Purpose: Traumatic brain injury (TBI) is a common cause of acquired epilepsy. The risk of seizure recurrence/epilepsy after a first seizure in patients with previous TBI remains uncertain. The purpose of this investigation was to use administrative data to investigate the risk of epilepsy in individuals after TBI with a first seizure, to identify subgroups potentially fulfilling the 2014 International League Against Epilepsy definition of epilepsy already after a first seizure.

Method: A register-based, retrospective cohort study. All individuals hospitalized in Sweden after TBI (n=111947) between 2000-2010 without prior seizures were identified, as well as 3 controls per case without TBI. Individuals with a first seizure code from the trauma were identified. In this group, we investigated the risk of a subsequent ICD-10 code of epilepsy diagnosis within 10 years using Kaplan-Meier analysis. Stratified analyses for age, sex and TBI severity were also performed.

Results: In our preliminary results, the risk for epilepsy after TBI and a first seizure code was approximately 40 %. In stratified analyses, a risk of approximately 60 % for epilepsy was identified among individuals after focal cerebral injuries. The risk for epilepsy after other structural injuries was slightly lower. After mild TBI (concussion), the risk was similar to the risk in the control group.

Conclusion: The risk of epilepsy in individuals with a first seizure after TBI depends on TBI severity. More studies are needed to identify subgroups of patients with severe TBI that fulfil epilepsy criteria already after a first unprovoked seizure. For those with a first seizure after concussion/mild TBI, the risk of epilepsy does not seem to be elevated.

Determinants of medication adherence in people with epilepsy: a multicentric, cross-sectional and observational study

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Purpose: Non-adherence to treatment in people with epilepsy (PwE) is cause of increased mortality, hospitalization and reduced quality of life and represents a challenge for clinicians. We realized an extensive survey to define clinical, demographic and neuropsychological factors that could influence medication adherence in PwE evaluated with the Morisky Medication Adherence Scale (MMAS-8).

Method: We performed a multicentric, observational and cross-sectional study where a population of 200 PwE was asked to answer online questionnaires containing the following clinical scales: MMAS-8, QoLIE (Quality of Life in Epilepsy Inventory), BDI-II (Beck Depression Inventory), GAD (Generalized Anxiety Disorder) and Resilience. We used ANOVA test and Pearson correlation to evaluate the relationship between medication adherence and demographic, clinical (seizure frequency, number of Anti-seizure Medications) and neuropsychological characteristics. We trained separate machine learning models (logistic regression, random forest, support vector machine) to classify patients with medium-high adherence (MMAS≥6) and poor adherence (MMAS<6) and identify the principal variables that influence medication adherence.

Results: We found that women were more adherent to therapy than men (p-value = 0.03577). MMAS-8 showed direct correlation with QoLIE-31 (p-value=0.01); Resilience (p-value=0.001), age (p-value=0.001), inverse correlation with BDI (p-value=0.001) and GAD (p-value=0.001). We also evidenced that the principal variables on decision scores were subitems of QoLIE-31 and individual characteristics as age, resilience, GAD, years of school, disease duration.

Conclusion: Our study confirms that women are more adherent to therapy than men and that older age is directly correlated with a major adherence. Interestingly, we found that psychological and resilience factors seem to play an important role in determining therapeutic adherence in PwE. Indeed, PwE with higher scores of BDI and GAD, lower resilience and quality of life tend to have scarce adherence compared to those with opposite characteristics.
Epilepsy and multiple sclerosis: clinical, radiological, electrophysiological and neuropsychological aspects

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Background: Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the central nervous system. Although inflammatory lesions of the white matter are the hallmark of the disease, several neuropathological and imaging studies have confirmed that grey matter is also involved in the disease. Epilepsy is three times more frequent in patients with MS when compared to the general population. The pathophysiological reason for this higher incidence is still unknown, even though the involvement of the cortical and deep grey matter could play a central role in seizures’ generation. Focal and focal-to-bilateral seizures are the most frequent although they can be misdiagnosed as paroxysmal demyelination events causing a delay in diagnosis and treatment. This study aims to investigate clinical, radiological, electrophysiological and neuropsychological aspects between epileptic MS patients and non-epileptic MS patients.

Methods: Eighteen MS patients with epilepsy (EPI+ group) and 18 age-and-sex-matched MS patients (EPI-group) were retrospectively selected from the database of the Multiple Sclerosis Center at the “SS. Annunziata” Hospital in Chieti. Patients underwent a comprehensive clinical assessment consisting of neurological examination, electroencephalogram (EEG), MRI and neuropsychological testing via the BICAMS (Brief International Cognitive Assessment for MS) - a set of 3 tests to assess cognitive domains: Information elaboration speed (SDMT), Verbal Memory (CVLT-II), Visuospatial memory (BVMT-R).

Results: EPI+ group showed a significantly higher EDSS (p=0.048), a higher amount of cortical and juxtacortical T2+ lesions (p=0.001) and performed worse in SDMT (p=0.046) and BVMT-R (p=0.049), compared to the EPI-group. Intercital EEG recording showed epileptiform abnormalities in 10/18 patients in EPI+ group compared to 0/18 in EPI-group.

Conclusions: Epilepsy causes an increase in disability (EDSS) and worse neuropsychological score in MS patients suggesting the need for earlier diagnosis and precocious treatment. Intercital EEG recording can be helpful for diagnosis.

Sleep architecture, interictal epiieptiform discharges and sleep co-morbidities in patients with progressive myoclonus epilepsy type 1 (EPM1)

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Purpose: Patients with progressive myoclonus epilepsy type 1 (EPM1) are having generalized tonic-clonic seizures and disabling myoclonic jerks that are more severe in the morning. Drowsiness also provokes myoclonus. We aimed to characterize sleep patterns, presence of the interictal epileptiform discharges (IEDs) and the prevalence of sleep co-morbidities such as Obstructive Sleep Apnea (OSA) and Periodic Limb Movements (PLM).

Methods: Twenty genetically confirmed EPM1 patients (7 male and 13 female aged 28.8 ±8.2 years) underwent overnight polysomnography, which included 19-channel EEG, standard polysomnographic channels and video. Experienced clinical neurophysiologist manually scored sleep stages, visually identified IEDs and scored and calculated Apnea/Hypopnea Index (AHI) and PLM Index. Obtained results were correlated with the main clinical characteristics and myoclonus severity assessed using Unified Myoclonus Rating Scale (UMRS).

Results: On average proportion of NREM and REM sleep stages in EPM1 patients was as following: N1 8.1%, N2 55.4%, N3 27.7% and REM 8.8%. Sleep latency was normal (14.4 ±14.5 minutes) and sleep-onset REM latency was prolonged (163.3 ±67 minutes) when compared to published normal values in healthy adults (Boulos et al. Lancet Respir Med 2019;7:533-43). Decrease in REM sleep proportion significantly correlated with earlier disease onset (r=0.569, p=0.009) and more severe myoclonus (-0.616, p=0.006). REM sleep amount was especially decreased in four compound heterozygous EPM1 patients (REM% 3.7 ±2.3% in compound heterozygotes and 10.0 ±3.9% in dodecamer expansion homozygous patients). Moderate or severe OSA (AHI>15) was detected in three patients. There was no clinically significant PLM in EPM1 patients. IEDs were observed during wakefulness and sleep.

Conclusion: We observed that earlier disease onset, more severe daytime myoclonus and genetic background of EPM1 seems to be associated with fragmented sleep architecture, especially reduction of REM sleep. The results imply the need to treat also sleep disturbances as part of the comprehensive care of EPM1.
Post-stroke epilepsy in children is rare and often not stroke-related: data from the Swiss Neuropediatric Stroke Registry

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Objective: To determine the incidence and causes of epileptic seizures in children suffering from arterial ischemic stroke (CAIS) to improve post-stroke follow-up and treatment of post-stroke epilepsy (PSE).

Methods: Children with CAIS were prospectively enrolled in the population-based Swiss Neuropediatric Stroke Registry (SNPRS) between 2000 – 2018. Their data was analyzed in the acute stage as well as 6- and 24-months post-stroke.

Results: Two hundred ninety-nine children met the inclusion criteria. No data about seizures was available in 4 children. Seizures were seen in the acute stage (within the first 7 days) in 24.1% (71/295), being the manifesting symptom in 50.1% (36/71). Children with seizures were younger (median [IQR] age 1.1 [0.4 – 5.1] years) than those without (median [IQR] age 6.9[3.8 – 12.1] years; p<0.001).

Conclusions: Persisting or new epileptic seizures after stroke are rare and often related to an underlying disease. Therefore, early reduction of anti-epileptic drugs after stroke in favor of rehabilitation might be safe.

Seizures and epilepsy in patients with neonatal arterial ischemic stroke: preliminary results from the Italian Registry of Infantile Thrombosis

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Purpose: to characterize acute seizures and post-stroke epilepsy in patients with Neonatal Arterial Ischemic Stroke (NAIS) included in the Italian Registry of Infantile Thrombosis (RITI).

Method: we performed a retrospective analysis of clinical manifestations, cerebral regions involved, electroencephalographic features, and treatment of acute seizures in an initial cohort of 242 patients with NAIS, born at term and pre-term, enrolled between 2010 and 2021 in 33 Italian centers. To study epilepsy, an additional form about epilepsy in RITI and the collection of data for neuropsychological assessment were integrated into RITI after it was tested in 56 patients from three centers of Padova, Roma, and Sassari. The neurodevelopmental outcome was prospectively assessed during the last follow-up.

Results: focal motor seizures were the most common symptoms of NAIS (40%); status epilepticus appeared in 26%. 72% were in monotherapy, in particular with Phenobarbital (90%). Cerebral lesions, interictal anomalies, and epileptic discharges on EEG were focal or multifocal, mainly left-sided. Epilepsy was diagnosed at a mean age of 2.5 years in six of 56 patients for whom this data was available (11%). All patients had focal motor seizures and 67% had had acute seizures as the first clinical manifestation of NAIS. 67% took polytherapy with good response in 67% and seizure-freedom in 50%. One patient underwent hemispherotomy. At the last follow-up of three years, the neurodevelopmental assessment was normal in 71% of the whole sample (n=112) and mostly abnormal (PSOM score ≥ 2 in 50%; 0.5-1.5 in 50%) in patients with epilepsy.

Conclusions: this is the first multicenter Italian study focused on acute and post-neonatal seizures in a large, general Italian sample with NAIS. The inclusion of an additional form about epilepsy in RITI and the collection of data for all NAIS patients in the registry will allow the in-depth analysis of the phenomenon and the consolidation of these preliminary results.
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Development of seizures in children undergoing stem cell transplantation

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Purpose: To describe the development of seizures in children undergoing stem cell transplantation (SCT), their associated risk factors, etiology and prognosis.

Method: Retrospective study of patients undergoing SCT in the Pediatric SCT Unit of the Hospital Sant Pau, Barcelona (2002-2018).

Results: Among the 178 patients, 26 (14.6%) developed seizures at some point during the SCT procedure and up to 2 years later, of which 9 were consequently diagnosed of a central nervous system (CNS) infection, 3 of a vascular disease and 8 of drug toxicity. A statistically significant association was found between seizing and the type of SCT performed (lower risk in familial identical donor, p=0.014), the development of a pre-engraftment syndrome (p=0.005), and both cytomegalovirus and Epstein-Barr reactivations (p=0.051 and p=0.046, respectively). Seizures predicted evolution to life-threatening complications and need for admission to the Intensive Care Unit (p<0.001) and higher mortality (p=0.039). A statistically significant association was also found between seizures and sequelae in survivors (p=0.029).

Children who developed seizures had a higher risk of CNS infection (odds ratio 23.81, IC95% 5.83-97.17) or vascular disease (odds ratio 5.77, IC95% 1.09-30.45).

Conclusion: Patients undergoing SCT from non-HLA-identical donors, especially if they have Cytomegalovirus or Epstein-Barr reactivations, or pre-engraftment syndrome, show a statistically significant association with seizures in our series. These patients can develop life-threatening neurological conditions, as CNS infections (risk 23.81 times higher compared to children without seizures) or vascular disease (risk 5.77 times higher), and show greater morbidity and mortality.

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Valproate-associated cerebral atrophy in children with epilepsy

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Purpose: Several case reports indicate brain atrophy during therapy with valproic acid (VPA), often accompanied by cognitive deterioration. Though, the prevalence of VPA-associated brain atrophy remains unknown. We therefore compared brain volume of children with epilepsy and VPA therapy to an age-matched group with epilepsy but without VPA.

Methods: After exclusion of patients with diseases associated with brain atrophy, 48 patients with- and 47 without VPA treatment were enrolled in this retrospective cohort study. 3D T1w datasets were automatically segmented into white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) using the SPM-12 algorithm. In a region of interest-based approach, volumes of cerebrum, cerebellum, and brainstem were read out, each subdivided into WM, GM, and CSF. Raw values were corrected to the total intracranial volume. Unpaired t-tests were used for group comparisons, Spearman’s correlation matrix for correlation of brain volume and VPA dose, VPA duration, disease duration, and age.

Results: There were no significant differences in age at MRI scan (VPA group 8.1 yrs. vs. control group 9.2 yrs., p=0.28), age at first seizure, disease duration, etiology, and sex. The VPA group showed significantly lower volumes in cerebral GM (p=0.0004), cerebral WM (p=0.0001), cerebellar GM (p<0.0001) and brainstem GM (p=0.025). None of the patients reported symptoms of cognitive decline at the time of MRI. No significant correlations were found between volume loss over time and age, duration of VPA therapy, dose at the time of MRI and disease duration.

Conclusions: Our data provide evidence that VPA therapy can lead to atrophy of the brain parenchyma in children with epilepsy. The volume loss might occur without clinical symptoms. Confirmatory studies in a prospective manner are needed with special focus on potential clinical symptoms as well as dose and duration of VPA.
Gain-of-function SCN1A variants cause spectrum of early onset epileptic encephalopathies that respond to sodium channel blocking therapies

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Purpose: Brain voltage-gated sodium channel Nav1.1 (SCN1A) loss-of-function variants cause the severe epilepsy Dravet syndrome and genetic epilepsy with febrile seizures plus (GEFS+). Gain-of-function SCN1A variants are associated with familial hemiplegic migraine type 3 (FHM3). Recently, novel SCN1A-related phenotypes have been described, including early infantile developmental and epileptic encephalopathy (DEE) with movement disorder (MD) and arthrogryposis. The underlying disease mechanisms, clinical spectrum, and treatment responses in these conditions are currently unknown. We describe a clinical, genetic and functional evaluation of affected individuals.

Method: Patients were ascertained via an international network using structured clinical questionnaires and from the literature. We compared sodium channels containing wild-type versus variant NaV1.1 subunits using whole-cell voltage clamp electrophysiological recordings in a heterologous mammalian system (tsA201-cells).

Results: Forty-six patients were included harbouring 33 different variants, 15 of which were biophysically characterised and 18 underwent in-silico functional prediction. The most severely affected infants (n=13) presented with congenital arthrogryposis, epilepsy onset within 3 days of life, tonic seizures and apnoeas, accompanied by a significant MD, profound intellectual disability and significant mortality. Twenty-one patients presented later, between 2 weeks and 3 months, with early infantile DEE and MD, and one patient presented after 3 months with DEE only. Eleven patients presented with FHM3. Associated SCN1A variants appear to cluster in regions of channel inactivation and biophysical recordings show evidence of gain-of-function properties. Clinically, 13 out of 16 (81%) gain-of-function variants were associated with a response to sodium channel blocker treatment without evidence of symptom exacerbation.

Conclusion: SCN1A gain-of-function mutations underlie a disease spectrum ranging from the previously undescribed early infantile DEE with MD and arthrogryposis (DEEMA) to DEE with or without MD and FHM3. Our study expands the spectrum of gain-of-function SCN1A-related phenotypes, defines key clinical features, provides insights into the underlying disease mechanisms and identifies potentially efficacious therapies.
Old drugs, new indications: efficacy of amantadine for refractory absences and electrical status epilepticus in sleep in children

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Purpose: Amantadine is currently a treatment of Parkinson’s disease, drug-induced extrapyramidal disorders, and influenza A prophylaxis. Some authors have reported its efficacy as an antiepileptic drug due to anti-NMDA and dopaminergic effect and has been used successfully in children with absence and myoclonic refractory seizures or electrical status epilepticus in sleep (ESES).

Method: We conducted a retrospective study of children treated with amantadine in a Pediatric Hospital in Madrid (Spain) for the last three years.

Results: We analyzed 10 children (5 women: 5 male) who were treated with amantadine at a mean age of 8 years (3-11), 4.8 years (1-8) from the onset of epilepsy. The epilepsy of all of them was refractory, the mean number of antiepileptic drugs used before amantadine was 9.4 (6-14), ketogenic diet was used in nine of them. The epilepsy was idiopathic with normal magnetic resonance images. The epileptic syndrome was ESES in 4 and generalized epilepsies in 6: refractory absence 3-3.5 Hz epilepsy in four; Jeavons Syndrome in one patient and Lennox-Gastaut syndrome in another patient. Amantadine was added to another antiepileptic drugs (mean number antiepileptic: 2.7) at a mean dose of 5.6 mg/kg/day each 12-24 hours, maximum of 300 mg/day.

In the ESES group, amantadine was effective in 3/4 (75%) for electroencephalogram normalization and seizure control (myoclonic and absence seizures). In the Generalized-Epilepsy Group, amantadine was effective for seizures control (75-99% response) in only one patient with refractory absence. The responding patients had not relapses in seizures or worsening of EEG during follow up for more than two years. One patient (10%) reported secondary effects (irritability and insomnia) and amantadine was withdrawn.

Conclusion: Amantadine can be an effective and safe treatment for drug-resistant generalized epilepsies in children: refractory absences and ESES.

Status Epilepticus 12:00-13:30
Tuesday, 12 July 2022
Room C

Spectrum of peri-ictal MRI abnormalities in status epilepticus

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Background: Status epilepticus (SE) can be associated with peri-ictal MRI abnormalities (PMA). PMA frequently affect cerebral cortex, hippocampus, pulvinar of thalamus, corpus callosum and cerebellum. In this prospective study, we aimed to characterize the spectrum of PMA in a large cohort of patients with SE.

Methods: We prospectively recruited 206 patients with SE between 20.02.2019 and 20.11.2021 who underwent an acute MRI at our institution. The standard MRI protocol included diffusion weighed imaging (DWI), fluid attenuated inversion recovery (FLAIR), arterial spin labelling (ASL) and T1-weighted imaging pre- and post-contrast application. The occurrence of PMA in each sequence was assessed. In terms of location, PMA were stratified as either cortical or subcortical. Amygdala, hippocampus, cerebellum and corpus callosum were regarded as subcortical structures.

Results: PMA were observed in 45% (93/206) of patients in at least one MRI sequence. DWI restriction was observed in 27% of patients. DWI lesion was mainly unilateral (75%). It affected cortical structures in 45%, subcortical structures in 36% and both, cortical and subcortical areas in 19% of patients. Cortical DWI lesions were located mostly in frontal lobes (60%); subcortical diffusion restriction affected either pulvinar of thalamus or hippocampus (95%). Alterations in FLAIR were observed in 18% of patients. FLAIR lesions were mainly unilateral (65%); cortical (49%) or subcortical (43%). FLAIR alterations were observed in both cortical and subcortical structures in 8% of patients. In ASL, 37% of patients had alterations, the vast majority of which were represented by ictal hyperperfusion (96%). Hyperperfused areas were located mainly in the cerebral cortex (88%) and were overwhelmingly unilateral (84%).

Conclusions: In our cohort, PMA were seen mainly in ASL, DWI and FLAIR. The most prevalent PMA was ictal hyperperfusion followed by DWI restriction and FLAIR abnormalities. Cerebral cortex was most frequently affected, especially frontal lobes. The majority of PMA were unilateral.
Peri-ictal MRI abnormalities in status epilepticus: is there an optimal time window for an acute MRI?

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Purpose: Status epilepticus (SE) may be associated with peri-ictal MRI abnormalities (PMA). The exact timing of occurrence of PMA in different MRI sequences remains unclear. In this prospective study, we aimed to determine the optimal timing of an acute MRI in patients with SE.

Method: We prospectively recruited 206 patients with SE who underwent an acute MRI with diffusion weighted imaging (DWI), fluid attenuated inversion recovery (FLAIR) and arterial spin labelling (ASL). We divided patients into four groups based on time intervals when MRI was performed after SE onset: 0-24 hours (group 1), 24-48 hours (group 2), 48-72 hours (group 3) and > 72 hours (group 4). The percentage of abnormalities occurring in each time interval in each MRI sequence was calculated.

Results: In total, PMA was observed in 45% (93/206) of patients with SE. In group 1, 35% of patients showed local areas of hyperperfusion, 25% had diffusion restriction and 18% - signal increase in FLAIR. In group 2, the chances of registering ictal hyperperfusion were the highest – 54%. In this group, diffusion restriction was seen in 29% and FLAIR hyperintensity in 24%. After 48 h (group 3), the chances of observing ictal hyperperfusion declined – 13%, but the rates of diffusion restriction (26%) and FLAIR hyperintensity (21%) remained unchanged. In the group 4 the chances of registering SE-associated diffusion restriction and FLAIR lesion were 38% and 31%, respectively. In this group, hyperperfusion was observed in 23% of patients.

Conclusion: In SE, ictal hyperperfusion on MRI is best seen in the first 48 hours after SE onset. SE-associated diffusion restriction and FLAIR hyperintensity remain relatively constant during the first 72 hours after SE onset. The best time window for performing MRI in patients with SE in our cohort was the first 48 hours after the onset of SE.

Machine-learning validation of the Epidemiology-based Mortality score in Status Epilepticus (EMSE)

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Purpose: To validate the value of the Epidemiology-based Mortality score in Status Epilepticus (EMSE) in predicting the risk of death at 30 days in a large cohort of patients with status epilepticus (SE) using a machine-learning system.

Method: We included consecutive patients with SE admitted from 2013 to 2021 at Modena Academic Hospital. A decision tree analysis was performed using the 30-day mortality as a dependent variable and the EMSE predictors as input variables. We evaluated the accuracy of EMSE in predicting 30-day mortality using the area under the receiver operating characteristic curve (AUC ROC), with 95% confidence interval (CI).

Results: 711 patients with SE were included, with a 30-day mortality of 28.1% (200/711). The median EMSE value in the entire population was 54 (interquartile range IQR, 30-86); it was lower in surviving compared to deceased patients (42, IQR 24-70 versus 86, IQR 62-114; p <0.001). EMSE was accurate in predicting 30-day mortality, with an AUC ROC of 0.786 (CI 95% 0.751-0.820), confirmed by bootstrap resampling. Etiology was the most relevant predictor (chi-square 113,349; df = 3), followed by age, EEG pattern and comorbidity. Certain etiologies and an age <40 years were associated with survival, whereas other etiologies, age >70 years and first EMSE comorbidity group predicted a 30-day mortality >60%. The decision tree analysis using EMSE variables correctly predicted the risk of mortality in 77.9% of cases; the prediction was accurate in 90% of surviving and in 47% of deceased patients within 30 days after the SE.

Conclusion: This validation study using a machine-learning system shows that EMSE is a valuable prognostic tool, and appears particularly accurate and effective in identifying patients with 30-day survival (high negative predictive value). Its predictive value for 30-day mortality is lower and needs to be further implemented.
External validation of the Status Epilepticus Severity Score (STESS) to predict mortality: a machine-learning analysis

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Purpose: To validate the value of the Status Epilepticus Severity Score (STESS) in predicting the risk of death at 30 days in patients with status epilepticus (SE) using a machine-learning system.

Method: We included consecutive patients with SE admitted from 2013 to 2021 at Modena Academic Hospital. A decision tree analysis was performed using the 30-day mortality as a dependent variable and the STESS predictors as input variables. We evaluated the accuracy of STESS in predicting 30-day mortality using the area under the receiver operating characteristic curve (AUC ROC), with 95% confidence interval (CI).

Results: 711 patients with SE were included, with a 30-day mortality of 28.1% (200/711). The median STESS value in the entire population was 3 (interquartile range IQR, 2-5); it was lower in surviving compared to deceased patients (3, IQR 2-4 versus 4, IQR 3-6; p <0.001). 88.1% (178/202) of deceased patients had scores of 3-6, whereas 11.9% (24/202) had scores of 0-2 (p <0.001). STESS was accurate in predicting 30-day mortality, with an AUC ROC of 0.740 (95% CI 0.700-0.779), only slightly reduced after bootstrap resampling. The most significant predictor was the seizure type (chi-square 72,374), followed by age. Non-convulsive SE in coma and age ≥65 years predicted higher risk of mortality, whereas generalized-convulsive SE and age <65 years was associated with lower risk of death. The decision tree analysis using STESS variables correctly predicted mortality in 88.6% of surviving and in 41.6% of deceased patients within 30 days after the SE, with an overall risk of error of 24.8%.

Conclusion: This validation study using a machine-learning system shows that STESS is a valuable prognostic tool, and appears particularly accurate and effective in identifying patients with 30-day survival (high negative predictive value). Its predictive value for 30-day mortality is lower and needs to be further implemented.

EEG seizures onset patterns and duration in focal status epilepticus

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Purpose: EEG studies characterizing the seizure-onset (SOn) patterns in status epilepticus (SE) are lacking. We aim to classify the different SOn patterns and seizures duration during focal SE and to evaluate any differences in mortality, morbidity and treatment response across different patterns.

Methods: consecutive scalp EEG recordings from adult patients admitted for focal SE, from January 2015 to August 2019 were reviewed. SOn patterns were identified according to Tanaka et al. (2018). For each patient 1 to 5 seizures were analyzed, and each seizure’s duration was recorded. The SOn pattern and duration of isolated focal seizures in patients admitted to the epilepsy monitoring unit (EMU) from January 2020 to August 2021 were reviewed and served as comparison group.

Results: 307 focal seizures were analyzed in 100 consecutive SE episodes with a median seizure duration of 90 sec (IQR: 136 sec); 121 isolated focal seizures in 42 epilepsy patients were recorded with a median duration of 60 sec (IQR: 55 sec)(p < 0.001). The most frequent SOn patterns in SE were repetitive epileptiform discharges (pattern #3; 39 patients; 105 seizures). Seizures with SOn pattern #3 showed longest duration (maximum duration 1200 seconds) compared to other SOn patterns (p = 0.04). No difference in demographics, SE etiology, semeiology and treatment response was observed; while patients older than 75 years showing SOn #3 had a significantly high risk for 30 days mortality (HR 4.059; 95% CI 1.508-10.924, p= 0.006).

Conclusions: Repetitive focal seizures within a SE episode had a longer median duration compared to focal seizures recorded in the EMU in accordance with the hypothesis that during SE mechanisms that lead to seizure termination are impaired. This was especially evident for SOn pattern#3. Analysis of SOn patterns can improve our understanding on SE mechanism and could become a useful EEG biomarker.
Etiology of status epilepticus and its relation with peri-ictal MRI abnormalities

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Background: Status epilepticus (SE) is a neurological emergency associated with high morbidity and mortality. Etiology is one of the most important factors determining the outcome of SE. Peri-ictal MRI abnormalities (PMA) are frequently associated with SE. In this prospective study we aimed to investigate whether certain etiologies of SE are associated with a risk of developing PMA.

Methods: Between 20.02.2019 and 20.11.2021, we prospectively recruited 206 patients with electro-clinical diagnosis of SE who underwent an acute MRI due to clinical needs at our institution with a standard SE protocol.

Results: PMA were observed in 45% (93/206) of patients. In our cohort of patients, cerebrovascular disease - 24% (50/206) was the most prevalent etiology for SE followed by intracranial tumors 19% (39/206) and cryptogenic 12% (24/206). In the group of patients with cerebrovascular disease, 52% (26/50) had PMA. However, in patients with intracranial tumor we observed that only 30% (12/39) showed PMA. In the cryptogenic group 54% (13/24) of patients had abnormal MRI.

In the cerebrovascular group, patients with hemorrhage as well as either acute or subacute stroke were most frequently associated with PMA, representing 77% (20/26) of cases.

Conclusions: In our cohort, over half of patients with either cryptogenic SE or SE due to cerebrovascular disease, had PMA. Acute/ subacute stroke and hemorrhage were the most frequent etiologies associated with PMA.

Pharmacological treatment influences multidien cycles in focal epilepsy

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Introduction: In refractory focal epilepsy, cycles of epileptic brain activity influence seizures over multi-day (multidien) timescales, but the effect of treatment on these cycles and their link to seizure rates is unknown. We hypothesized that cycles of epileptic brain activity may vanish with successful pharmacological treatment.

Methods: Interictal epileptiform activity (IEA) was recorded over years in 163 participants in the RNS System clinical trials, who were implanted with an intracranial brain stimulator for detecting and treating seizures. Participants kept a seizure diary, and changes in medications were logged. Using a wavelet transform, we extracted underlying multidien cycles from recordings of IEA. We identified timepoints where a new anti-seizure medication (ASM) was started and compared seizure rates among epochs with present or absent multidien cycles of IEA after beginning ASM. This measure was evaluated for predictive power by the area under the curve (AUC) of the receiver operating characteristic.

Results: We identified 273 new ASM trials, of which 88 (32%) led to a >=50% decrease in seizure rate (responders). Relative seizure rate was significantly lower (p<0.05 Wilcoxon test) when multidien rhythms of IEA vanished after introduction of a new ASM. When measuring the sensitivity-specificity trade-off of using decreases in multidien rhythms of IEA as predictor for reduction in seizures at a 3-month horizon, we found an AUC of 0.61-0.69 when predicting 50-90% reduction of seizure rate, respectively. The same method yielded an AUC 0.70-0.72 when predicting 90% seizure reduction at 12 and 6 months.

Conclusion: In this cohort, vanishing of multidien cycles of IEA following the beginning of new ASM was consistently associated with reduced reported seizure rates for up to 12 months. Although causality cannot be established, this suggests that multidien IEA cycles may play an important role in seizure recurrence over long periods (months to years).
Awareness alteration in focal epilepsy is related to loss of signal complexity and information processing

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**Purpose:** Alteration of awareness is a main feature of temporal lobe epilepsy and efforts have been made to better understand the neurophysiological correlates. In this work, we studied how the information contained in EEG signals was modified during seizures with altered awareness. We used permutation entropy (PE) a measure of the complexity and the amount of information present in the signal.

**Method:** PE estimation was performed in thirty-six seizures of sixteen patients with temporal lobe epilepsy who underwent SEEG recordings. We tested whether altered awareness (based on the Consciousness Seizure Score, CSS) was correlated with a loss of signal complexity. We estimated global changes in PE as well as regional changes in order to gain insight into the mechanisms associated with awareness impairment.

**Results:** Our results reveal a positive correlation between the decrease of entropy and the consciousness score as well as the existence of a threshold on entropy that could discriminate seizures with no alteration of awareness from seizures with profound alteration of awareness. The loss of signal complexity was extended, affecting the associative cortices, in patients with profound alteration of awareness, while it was limited to the temporal mesial structures in patients with no alteration of awareness.

**Conclusion:** In summary, PE is a promising tool to discriminate between the different subgroups of awareness alteration in TLE.

Efficacy of perampanel in nocturnal seizures in adult patients with epilepsy

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**Purpose:** Nocturnal seizures represent a major problem in the treatment of epilepsy in adult patients. We aimed to study the effectiveness of perampanel for the treatment of nocturnal seizures in adult patients with epilepsy.

**Methods:** Observational study of a prospectively acquired sample of adult patients with epilepsy in which perampanel was started from January to October 2021 in a specialized epilepsy unit in a tertiary hospital. Demographics and clinical characteristics were recorded. All patients completed a follow-up period (FUP) of at least 3 months. Seizure frequency during the 6-month period before treatment initiation was obtained from medical records. Retention and responder rates (considered as a nocturnal seizure frequency reduction of ≥50%) and improvement of subjective sleep disturbances were analyzed as outcome measures.

**Results:** Forty-one patients were included (mean age 41.0±17.9; 58.5% male) of which 30 patients had a 6-month FUP. Focal epilepsy was the most common diagnosis (80.5%) and most patients had a structural etiology (56.1%). Twenty-eight patients (68.3%) had drug-resistant epilepsy. Mean nocturnal seizure frequency per month at baseline was 10.6±28.2. Thirteen patients (31.7%) had subjective sleep disturbances at baseline, of which insomnia was the most frequent complaint (17.1%). Perampanel was started at a median dose of 4mg/day (range= 2-14). At 3-month FUP, retention rate was 78% and 65.9% were considered responders (51.2% were seizure-free). Nocturnal seizures monthly decreased significantly at 6-month FUP (6.6±0.4 vs 10.6±28.2 seizures/month; p=0.045). Subjective sleep disturbances improved at 3-month FUP (12.2% vs 33.3%; p= 0.008).

**Conclusions:** Perampanel can be a suitable treatment option in adult patients with epilepsy with nocturnal seizures, and can improve the presence of sleep disturbances.
Cavum septum pellucidum on MRI is a marker of generalised convulsive epilepsy

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Purpose: Cavum septum pellucidum (CSP) usually closes between 6 months gestation to 2 months post-term. Non-closure of the septum pellucidum is considered a normal variant, with prevalence of 0.79-5.5%. CSP secondary to head trauma is well recognised and has a direct relationship to cerebral volume loss and poorer cognitive outcomes. There is very little published on CSP in epilepsy, other than case reports and small centre studies. We reviewed the incidence of CSP in patients admitted to our Epilepsy Monitoring Unit (EMU) over a four-year period, relative to epilepsy classification (ILAE 2017).

Methods: We reviewed MRI neuroimaging on 442 patients admitted to the EMU at Beaumont Hospital, Ireland from 2016 – 2020. Epilepsy classification at discharge, alternate diagnoses (Non-epileptic attack disorder [NEAD] or other pathology [syncope, parasomnia or stereotyped behavioural events]), and inconclusive studies were recorded. Only patients with available MRI studies were included. Patients were then stratified into those with CSP on MRI.

Results: Of the 442 patients, 396 had MRI imaging available and were included in the study. Patients studied had an age range of 16-82 years (mean 40 years), with 60% being female. A diagnosis of epilepsy was established in 222 patients. NEAD was diagnosed in 105 patients, 20 had other pathology and 58 had inconclusive studies.

In our epilepsy cohort, 47.7% had CSP vs. 21% in other groups. In those with both epilepsy and CSP, 75% had a documented history of generalised tonic-clonic seizures.

Conclusion: In our study, individuals with epilepsy had higher rates of CSP compared to the general population (47.7% vs. 0.7-5.5%). The majority of patients with epilepsy and CSP experienced generalised convulsions (75%). This suggests that CSP is an anatomic marker of uncontrolled convulsive epilepsy. These findings should prompt greater awareness of CSP during initial patient evaluation and epilepsy classification.

Psychiatric and cognitive adverse events of eslicarbazepine acetate (ESL) monotherapy on adults with focal seizures: results from a randomized, double-blind, active-controlled study and a 2-year open-label extension study

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Purpose: Evaluate the incidence of psychiatric and cognitive adverse events (AEs) of eslicarbazepine acetate (ESL) monotherapy in adult patients with focal seizures (FS).

Methods: Study -311 was a phase III, randomized, double-blind (DB), active-controlled (Carbamazepine, CBZ-CR), non-inferiority study, followed by a 2-year open-label extension (OLE). Study- 311/EXT. Subjects treated with ESL in DB continued with ESL (ESL/ESL) and subjects treated with CBZ-CR in DB were switched to ESL (CBZ-CR/ESL) during the OLE study. Psychiatric treatment-emergent AEs (TEAEs) and TEAEs affecting cognition were retrieved.

Results: DB safety population contained 813 patients (401 ESL; 412 CBZ-CR), of which 184 received ESL monotherapy throughout the OLE study (ESL/ESL, n=96; CBZ-CR/ESL, n=88). During DB, psychiatric TEAEs were reported by 14.7% and 17.5% of patients in ESL and CBZ-CR groups; related TEAEs: 4.0% (ESL) and 4.4% (CBZ-CR) of patients; most frequently related TEAEs: anxiety (ESL: 0.7%; CBZ-CR: 0.5%), confusional state (ESL: 0.2%; CBZ-CR: 0.5%), depressed mood (ESL: 0.7%; CBZ-CR: 0.5%), depression (ESL: 0.7%; CBZ-CR: 0.0%), insomnia (ESL: 0.0%; CBZ-CR: 0.7%) and mood altered (ESL: 0.5%; CBZ-CR: 0.0%). In OLE, psychiatric TEAEs were reported by 2.1% (ESL/ESL) and 3.4% (CBZ-CR/ESL) of patients and no related psychiatric TEAEs were reported.

Cognitive TEAEs were reported by 8.5% of patients in ESL and CBZ-CR groups during DB; related TEAEs: 5.0% (ESL) and 2.9% (CBZ-CR) of patients; most frequently related TEAEs: cognitive disorder (ESL: 0.2%; CBZ-CR: 0.7%), disturbance in attention (ESL: 1.7%; CBZ-CR: 0.5%), memory impairment (ESL: 1.5%; CBZ-CR: 1.0%) and irritability (ESL: 0.5%; CBZ-CR: 0.5%). In OLE, cognitive TEAEs were reported by 2.1% (ESL/ESL) and 2.3% (CBZ-CR/ESL) of patients; related cognitive related TEAEs were reported in 1.1% (ESL/ESL) and 1.0% (CBZ-CR/ESL) of patients.

Conclusion: In this phase III, DB trial with OLE the analysis of psychiatric and cognitive TEAEs was consistent with the known safety profile of adjunctive ESL. It showed that adult patients with FS who took ESL in monotherapy on long-term treatment reported a low incidence of psychiatric and cognitive TEAEs.
Duration of postictal impaired awareness after bilateral tonic-clonic seizures: EEG and patient characteristics

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Purpose: Ictal and postictal phenomena that may impact the duration of postictal impaired awareness have not been well studied. Postictal unresponsiveness invariably occurs following bilateral tonic-clonic seizures (BTCS). BTCS are a major risk factor for sudden unexpected death in epilepsy (SUDEP). We quantify the effects of seizure characteristics on postictal recovery of awareness following BTCS. Factors include: the total seizure duration, the duration of the tonic phase of a BTCS, presence of postictal generalized EEG suppression (PGES), duration of postictal tonic electromyographic discharge, peri-ictal respiratory dysfunction, patient age, duration of epilepsy, and gender.

Method: Fifty-eight patients admitted to the epilepsy monitoring unit with BTCS were studied. Forty-one had unilateral onset temporal seizures. The remainder had bitemporal onset, extratemporal onsets, undetermined onsets, or were generalized at onset. Following the first BTCS, time to initial recovery of awareness and its possible association with patient and seizure characteristics as well as peri-ictal respiratory dysfunction were evaluated. The presence or absence of postictal agitation was noted.

Results: The severity of respiratory dysfunction and seizure characteristics were not associated with time to initial recovery of awareness. A shorter time to recovery of awareness was significantly associated with a younger age (p=0.007). Postictal agitation was more common in males (p=0.023).

Conclusion: Focal seizures may impair awareness by active inhibition of subcortical arousal mechanisms. Focal seizures progressing to bilateral tonic-clonic seizures (BTCS) result in further widespread cerebral dysfunction impacting postictal awareness. MRI studies show accelerated brain aging in patients with temporal lobe epilepsy. Our findings suggest that patient age, as a surrogate marker for the lifetime burden of seizures, results in a progressive worsening in time to recovery after BTCS by an increasing negative impact on networks involved in arousal.

Clinical Neurophysiology 2
Tuesday, 12 July 2022
12:00-13:30
Room A

Generalised epileptic fast activity is a biomarker for changes in seizure frequency in Lennox-Gastaut syndrome

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Purpose: Generalised paroxysmal fast activity (GPFA) is a key electrographic feature of Lennox-Gastaut syndrome (LGS) and is quantifiable with EEG. We aimed to quantify the burden of GPFA in LGS throughout various stages of a deep brain stimulation (DBS) treatment trial (ESTEL trial: Electrical Stimulation of the Thalamus in Epilepsy of Lennox-Gastaut phenotype) and determine its association with diary-recorded seizure frequency. We hypothesised that changes in GPFA burden will predict changes in seizure frequency.

Methods: Seizure diaries and 24-hour EEG of 17 young adults with LGS (mean age±1SD=24.9±6.61; 13 females) from the ESTEL trial, were evaluated. Average seizures/day over four, three-month periods was determined from monthly seizure diaries. GPFA burden was manually quantified on four, 24-hour EEGs, performed at the end of each three-month study phase; number of discharges, their onset and duration over sleep (2-hours) was manually marked. Correlation between total GPFA and seizures/day was compared using a linear mixed effects model.

Results: Following ≥3-months DBS treatment, GPFA and diary-recorded seizures reduced. Both total duration and number of GPFA discharges positively correlated to diary-recorded seizure frequency over the ESTEL trial (P<0.001). At baseline, median diary-seizures (across all patients) was 2.64/day, compared with 284 electrographic seizures per day. Baseline median GPFA discharge rate was 4.73/minute (284/hour).

Conclusion: GPFA duration and frequency, measured over a two-hour period of sleep EEG is associated with diary-recorded seizure frequency over three-months in patients with LGS. Although the relationship between GPFA and seizure frequency varies greatly from patient to patient, within each individual, the ratio of GPFA to clinical seizure remains stable, and hence the burden of GPFA tracked treatment response in participants undergoing DBS treatment in the ESTEL trial. Given seizure diaries are difficult for caregivers to accurately maintain, we propose GPFA burden be used as a biomarker to monitor treatment response.
Patient-specific seizure forecasting using minimally-invasive subcutaneous EEG - a multicenter cohort analysis

**Purpose:** Seizure unpredictability is a major disabling aspect of living with chronic epilepsy. Cumulative research in the past decades has advanced our understanding of the dynamics of seizure risk. Technological advances have recently made it possible to record pertinent biological signals continuously, including EEG. We aimed to assess whether patient-specific seizure forecasting is possible using remote, minimally invasive ultra long-term subcutaneous EEG.

**Method:** A two-center cohort of ultra long-term subcutaneous EEG recordings was analyzed, including six patients with focal drug-resistant epilepsy monitored for 46 to 230 days with median 18 hours/day of recorded data, totaling over 11,000 hours of EEG. Total electrographic seizures identified by visual review ranged from 12 to 36 per patient. Three candidate subject-specific long short-term memory (LSTM) network deep learning classifiers were trained pseudo-prospectively on preictal (1-hour before) and interictal (more than one day apart from seizures) EEG.

**Results:** Significant forecasting performance was achieved in three to five out of six patients depending on each of the three different architectures. For each architecture, forecasts showed median area under the ROC curve (AUC) of 0.71, 0.68 and 0.74, median sensitivity of 68%, 71% and 73%, and median time in warning of 27.3%, 38.2% and 36.3%. Overall, the output of the forecasts closely followed patient-specific circadian patterns of seizure occurrence.

**Conclusion:** This study demonstrates proof-of-principle that subject-specific seizure forecasting using a minimally invasive subcutaneous EEG device capable of ultra long-term at-home recordings, is possible. These results are encouraging for the development of a prospective seizure forecasting trial with minimally-invasive EEG.

Quantitative analysis of EEG frequency composition in STXBP1 developmental epileptic encephalopathy

**STXBP1** gene is one of the major causes of early-onset Developmental and Epileptic Encephalopathy (DEE). However, the quantitative-EEG analysis (q-EEG) in **STXBP1**-DEE is a poorly explored field. Here, we investigate the regional differences in EEG frequency composition in **STXBP1**-DEE. We collected the electro-clinical data of subjects with **STXBP1**-DEE. The EEG analysis was based on visual assessment of whole traces, followed by frequency-domain analysis. We quantified the relative power (RP) of the major frequency bands (alpha, beta, theta, and delta), the spectral-edge-frequency (SEF), and the median dominant frequency (MDF). The analysis was performed on 10 seconds epochs in two electrode groups defined as anterior (Fp1-Fp2-F3-F4-F7-F8) and posterior (O1-O2-P3-P4-P7-P8). We confronted averages of all cited parameters in 60 epochs centered around the maximum RP in the delta band, divided by electrode group.

We analyzed 16 EEG traces in 12 patients (7 females / 5 males), of a mean age of 9.6 years (range: 7 months-29 years), each taking 1-2 anti-seizure medications (ASMs). The average SEF was 3.14 Hz (median 3.2 Hz) in the anterior electrodes and 3.64 Hz (median 3.64 Hz) posteriorly. The MDF was 1.83 Hz anteriorly, and 1.91 Hz posteriorly. The RP in the delta band was significantly higher than other bands (alpha - p>0.01; beta – p>0.05; theta – p>0.05) in the anterior regions, but not posteriorly in the alpha and beta bands.

We didn’t find significant correlation between anterior RP, the patients’ age, the epilepsy focus, and the concomitant ASMs.

Our findings show a diffuse abundance of the EEG frequencies in the delta band. The q-EEG analysis shows the predominance of this activity on other frequencies in the frontal regions. The lack of correlation between RP, patients’ age, epileptic activity, and concomitant medications suggests this activity might reflect a selective functional dysfunction of the fronto-temporal network in **STXBP1**-DEE.
Epileptic spasms are associated with increased SEEG derived functional connectivity in tuberous sclerosis complex

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Purpose: Epileptic Spasms (ES) are common in Tuberous Sclerosis Complex (TSC). However the underlying network alterations and relationship with epileptogenic tubers are poorly understood. We examined interictal functional connectivity (FC) using stereo-EEG (SEEG) in patients with TSC to investigate the relationship between tubers, epileptogenicity and ES

Method: We analysed 18 patients with TSC who underwent SEEG (mean age 11.5 years). The dominant tuber (DT) was defined as the most epileptogenic tuber using the Epileptogenicity Index. Epileptogenic Zone (EZ) organisation was quantitatively separated into focal (isolated DT) and complex (all other patterns). Using a 20 minute interictal recording, FC was estimated with non-linear regression, $h^2$. We calculated i) intrazone FC within all sampled tubers and normal appearing cortex and ii) interzone FC involving connections between DT, other tubers and normal cortex. The relationship between FC and i) EZ organisation, ii) ES as a current seizure type at the time of SEEG and iii) epileptogenicity was analysed using a mixed generalized linear model. Spike rate and distance between zones were considered in the model as covariates.

Results: Six patients had ES as a current seizure type at time of SEEG. ES patients had a great number of tubers and none had TSC1 mutations. The presence of ES as a current seizure type was independently associated with increased FC within both intrazone ($p = 0.033$) and interzone ($p = 0.011$) networks. Post-hoc analyses identified that increased FC was associated with ES across tuber and non-tuber networks. EZ organisation and biomarkers of epileptogenicity were not associated with FC.

Conclusion: Increased cortical synchrony amongst both tuber and non-tuber networks is characteristic of patients with ES and independent of both EZ organisation and tuber epileptogenicity. This raises the prospect of non-invasive FC biomarkers aiding treatment paradigms in TSC.
ENCEVIS automatic seizure detection - evaluation in the setting of epilepsy monitoring unit

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Purpose: Evaluation of efficacy and reliability of the automatic program ENCEVIS for seizure recognition and for screening EEG recordings with and without clinical seizures.

Method: Prospective evaluation of all long-term recordings (>4h.) at SEIN-SKUH Epilepsy Center in the period 06.2018- 06.2021 was carried out. All recordings containing at least one documented clinical seizure were included into the study.

ENCEVIS V17 was used for automatic seizure detection. Visual EEG analysis was carried out by two neurophysiologist according to the SCORE protocol. True/false positive and true/false negative seizure detection by ENCEVIS was taken into consideration.

Results: Overall, 451 recordings were performed, 255 recording were selected for final analysis. Per recording: False Positive (FP) 121 (47.5±50.0%), False Negative (FN) 1 (0.4±6.3%), P<0,005, True Positive (TP) 42 (16.5±37.2%) true Negative (TN) 104 (40.8±49.2%)

Total number of Visually documented seizures was 113 (from 42 ictal recordings).
ENCEVIS data: (TP) 58 (51.8±50.2%), (FN) 42 (48.2±50.2%), Seizures<10SEC: TP 1 (6.3±25.0%), TN-12 (93.7±25.0%), Seizure 10-60 second TP 34 (55.7±50.1%), FN- 31 (44.3±50.1%), Seizure >60 second: TP – 23(63.9±48.7%), FN – 12(36.1±48.7%) P<0,005.

Onset: frontal: total 55, TP-32 (56.4±0.50%), FN-24 (43.6±0.50%), P=0.19, Parietal/Occipital: Total-10 TP-8 (80.0±42.2%), FN-2 (20.0±42.2%), P=0.0052 , Temporal: Total – 39, TP-30 (76.9±42.7), FN-9 (23.1±42.7%), P<0.005,

Semiology: motor seizures – total 86, TP-51 (59.8±49.4%), FN-35 (40.7±49.4%), P=0.015, non-motor seizures Total-28, TP-7 (25.0±44.1%), FN-21 (75.0±44.1%), GTCS – 39, TP-12 (100%), FN-0 (0%), P=0.005.

Conclusion: Automatic seizure detection program ENCEVIS is a reliable tool to assist clinical neurophysiologist in screening EEG recordings with and without clinical seizures.
ENCEVIS shows high sensitivity for epilepsy originated from temporal lobe, GTCS and seizures with duration >60 sec.

What is the optimal duration of home-video-EEG monitoring for patients with less than daily seizures? A practical simulation study

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Purpose: Video-EEG monitoring (VEM) is an important tool for diagnosis of suspected epileptic seizures and for drug-resistant epilepsy (DRE) patients, but its use is limited by the low availability of inpatient facilities. Home VEM (HVEM) can increase availability and lower costs of monitoring, but its use is hindered, mainly by the difficulty of performing recordings longer than one week. Conversely, the necessary duration of monitoring is expected to be longer for HVEM users than for inpatients with genuine epileptic seizures, since treatment cannot be safely reduced. We aimed to obtain an estimated quantification of the required VEM length for capturing 1, 3 or 5 seizures (to cover various diagnostic scenarios encountered in clinical practice) in an ambulatory setting.

Method: We calculated the yield of VEM for capturing 1, 3 or 5 seizures in different days, among 100,000 simulated time-courses of epilepsy, representing patients with more than 1 and less than 30 seizures/month (89% of adults and 85% of children). The Matlab platform was used to build the simulations, given previously reported frequencies of seizures in adults and in children, and intermittent cycling of seizures in adults.

Results: The duration of HVEM needed to record 1, 3 or 5 seizures in 80% of children was 2, 5 and 8 weeks (median 2, 11 and 15 days), respectively, and significantly longer in adults (2, 6 and 10 weeks; median 3, 15 and 26 days; p <10^-10 for all comparisons).

Conclusion: Longer sessions of HVEM than currently in use are needed for expanding its clinical utilization from merely diagnosis of nonepileptic or very frequent epileptic events to a valuable tool for presurgical assessment of most patients with DRE. Technical developments and further prospective studies are warranted.

Disclosure: DE, MM and DE are involved in VIRDA startup company, developing very-long term HVEM systems
157 The influence of comorbidity on mortality in patients with epilepsy and psychogenic non-epileptic seizures

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Purpose: Mortality in psychogenic non-epileptic seizures (PNES) is not well studied, despite patients having an increased risk of death compared to the general population, with a similar magnitude to patients with epilepsy. This study aims to determine the risk factors contributing to excess PNES mortality.

Methods: This retrospective cohort study describes 1,628 Australian tertiary epilepsy outpatients and an 8:1 comparison cohort, matched by age, sex and socioeconomic status (SES) to national administrative databases between 2007-2017. Disease classification was by two independent epilepsy specialist raters from the medical record, including comprehensive epilepsy program meetings with 92% of typical PNES events captured in an epilepsy monitoring unit. Privacy-preserving data-linkage was undertaken with the national prescription, National Death Index, and National Coronal Information System. Comorbid diseases were derived by applying an Australian validated Rx-Risk algorithm to dispensed prescriptions. We fitted Cox proportional hazard models controlling for age, sex, SES, comorbidity, disease duration and the number of concomitant antiseizure medications (ASM), as a marker of disease severity.

Results: 13,488 participants were followed for a median of 3.2 years (IQR 2.4-4.0 years). The age-sex-SES-adjusted hazards ratio (95% confidence interval) was elevated for epilepsy 4.74 (3.36, 6.68) and PNES 3.46 (1.38, 8.68) and remained elevated for epilepsy 3.21 (2.22, 4.63) but not PNES 2.15 (0.77, 6.04), after comorbidity adjustment. PNES had more pre-existing comorbidities when compared to epilepsy and comparison groups (p=0.0007) with three times greater median weighted Rx-Risk score. Psychotic illness, opioid analgesia, malignancies, and non-opioid analgesia had the greatest influence on PNES comorbid risk.

Conclusion: Higher comorbidity appears to explain the excess PNES mortality and may either represent a wider under-recognised somatoform disorder or a psychological response to physical illness. Better understanding and the bidirectional relationship of these wider somatic treatments in PNES could potentially reduce the risk of death.

158 Adherence patterns in antiseizure medications influencing the risk of Sudden Unexplained Death in Epilepsy: a data linkage study using dispensed prescriptions

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Purpose: Medication adherence is considered an important risk factor for Sudden Unexplained Death in Epilepsy Patients (SUDEP) although measurement accuracy is elusive. This study aims to estimate antiseizure medication (ASM) adherence and identify adherence patterns that influence epilepsy mortality.

Methods: We retrospectively identified a cohort of <1,187 Australian tertiary epilepsy outpatients from 1/01/2012 until 31/12/2017. Privacy-preserving data-linkage with the national prescription, death, and coroner's databases were performed. We fitted a 4-cluster longitudinal group-based trajectory model for ASM adherence from recurring 90-day windows of prescription dispensations during a 3-year ‘landmark period,’ 1/1/2012 to 31/12/2014. Using the Adhere-R package. We estimated the risk of SUDEP and all-cause death for each adherence pattern during an ‘observation period,’ 1/1/2015 to 31/12/2017, using the Cox-proportional hazards and logistic regression models were adjusted for age, sex, socioeconomic status, epilepsy duration, comorbidity, epilepsy severity, and inadequate seizure control.

Results: <1,187 participants were observed for a median of 3.2 years (IQR 2.4-4.0 years). We observed <10 cases of SUDEP during the observation period. We identified 4 patterns of ASM adherence: good 51%, declining 24%, poor 16%, and very poor 9%. Declining adherence was associated with an increased risk for SUDEP, hazard ratio 8.43 (95%CI 1.10, 64.45) at 1 year, and HR 9.17 (95%CI 1.16, 72.21) at 3 years. Compared to no ASM therapeutic change, the addition of a 2nd to 4th ASM offered increased protection against SUDEP in patients with continuing drug-resistant epilepsy.

Conclusion: Poor adherence is underappreciated and observed in half of the outpatients with epilepsy. A declining pattern of adherence, observed in a quarter of patients, is associated with more than eight times the increased risk of SUDEP. Any ongoing therapeutic interventions must be coupled with strategies to maintain and improve patient ASM adherence if we are to reduce the risk of SUDEP.
Sudden unexpected death in epilepsy (SUDEP) in persons younger than 50 years – a retrospective nationwide cohort study in Denmark

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Purpose: Persons with epilepsy have an increased mortality including a high risk of sudden unexplained death (SUD), also referred to as sudden unexpected death in epilepsy (SUDEP). We aimed to evaluate the risk of SUDEP in comparison to other causes of death and the risk of SUD in persons with and without epilepsy.

Methods: We undertook a retrospective population-based cohort study of all Danish citizens with and without epilepsy aged 1-49 years during 2007-2009. All deaths in the population were evaluated and all cases of SUD identified. Primary causes of death in persons with epilepsy were evaluated independently by three neurologists and one neuro-paediatician, using the unified SUDEP criteria.

Results: The three most frequent causes of death in persons with epilepsy were cancer (2.38 per 1000 person-years), SUDEP (1.65 per 1000 person-years), and pneumonia (1.09 per 1000 person-years) compared with cancer (0.17 per 1000 person-years), accident-related deaths (0.14 per 1000 person-years), and cardiovascular disease (0.09 per 1000 person-years) in persons without epilepsy. Considering definite, definite plus, and probable cases, the SUDEP-incidence was 0.27 per 1000 person-years (95% CI 0.11–0.64) in children aged 1-17 years and 1.21 per 1000 person-years (95% CI 0.96–1.51) in adults aged 18-49 years. Adjusted for age and sex, persons with epilepsy younger than 50 years had a 10.8-fold (95% CI 9.97–11.64, p<0.0001) increased all-cause mortality and a 34.4-fold (95% CI 23.57–50.28, p<0.0001) increased risk of SUD compared with persons without epilepsy. SUDEP accounted for 23.3% of all SUD.

Conclusion: This nationwide study of all deaths in persons with epilepsy younger than 50 years found a lower SUDEP risk in children compared with adults, and that epilepsy was a major risk factor for SUD in the background population. This underlines the importance of addressing risk factors for SUDEP to prevent premature death.

The COVID-19 Pfizer BioNtech mRNA vaccine and the frequency of seizures

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Purpose: A nation-wide vaccination operation against Coronavirus disease 2019 (COVID-19) using the BNT162b2 mRNA vaccine commenced in Israel in December 2020. People older than 60 years were prioritized and shortly after, most of them were vaccinated. Seizures are not infrequently being attributed to the vaccine despite lack of supporting evidence. People with epilepsy (PWE) are often reluctant to get the vaccine due to concerns of seizure aggravation. We aim to examine the incidence of new onset seizures and the frequency of recurrent seizures in PWE before and after the introduction of the vaccine operation.

Method: All adults who presented to the emergency department (ED) of Tel Aviv Sourasky Medical Center between January 1st and May 31st 2017-2021 and diagnosed with seizure were included. Demographic, clinical, and vaccination status parameters were collected using MDClone, a data acquisition tool. Vaccination rates in the general population were obtained from official governmental publications. Statistics included sub-analysis of patients with the highest vaccination rate, people older than 60.

Results: 1675 cases were included. Numbers of ED visits and hospital admissions due to seizures in 2021 were comparable to preceding years after adjusting to the total number of ED visits at the same time. Out of 339 cases in 2021, 134 patients older than 60 years old presented to the ED (39.5%) compared to 124-151 in 2017-2019 (37-44%) and 103 in 2020 (33%). Vaccination rate among patients hospitalized due to seizures was similar to the general population of the same age group during the same period in Israel.

Conclusion: Despite very high vaccination rates in the general population in Israel and especially among people older than 60 years, no increase was observed in ED presentations due to seizures. We conclude that the mass vaccination with Pfizer BioNTech mRNA vaccine is not associated with increased seizure propensity.
Functional analysis of SCN1A non-canonical splice-site variants reveals high rate of false-positive causative variants

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Purpose: To create a full gene-splicing assay for all protein-coding exons of the SCN1A gene with the potential for functional evaluation of reported or newly described splicing variants in SCN1A gene for performing robust genotype-phenotype correlations.

Methods: Bioinformatic analysis of all reported variants in SCN1A in the professional version of HGMD database performed with SpliceAI. Mini and midigenes splicing system covering all 26 protein-coding exons of the SCN1A containing 1-5 exons were created on pSpl3-Flu splicing vector. Thesplicing pattern of wild-type mini/midigenes were evaluated 48 hours post transfection using RT-PCR. All tested variants were introduced using site-directed mutagenesis.

Results: Testing of wild-type plasmids containing all 26 protein coding exons of SCN1A gene revealed normal splicing pattern for only 9 exons. Correction of splicing pattern in wild type mini/midigenes for performed using several novel and previously described approaches– modulation of the genomic surrounding, decreasing plasmid promotor strength, mutagenesis of plasmid introns for U12 introns and mutagenesis of cryptic splicing sites. Testing of 62 non-canonical splice-site variants revealed different splicing alteration with exon skipping being the most frequent. Interestingly almost 20% of tested variants (11 out of 62) had no impact on splicing, although being reported as pathogenic/likely pathogenic in the literature. Testing of 10 missense and 1 nonsense variant predicted to disrupt splicing by SpliceAI, revealed that 8 are in fact splice-affecting.

Conclusion: Functional analysis of the majority of previously described non-canonical splice-site intronic variants revealed high rate of false-positive variants reported as pathogenic or likely pathogenic in the SCN1A gene. Moreover, we demonstrated that many coding variants are in fact splicing variants. This knowledge is essential for proper genetic counseling and can improve genotype-phenotype correlations in SCN1A-related epilepsy.

The phenotype of SCN8A-lof epilepsy and related disorders

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Purpose: We aim to describe the phenotype of SCN8A variants with loss-of-function (LOF) effect, to obtain data for early differential diagnosis and precision therapy management.

Method: From our database of 664 patients with SCN8A-disorders, we selected those carrying variants with confirmed LOF effect, including truncating variants and missense variants previously tested in vitro. We collected detailed demographic, genetic and electro-clinical data, including information about psychomotor development, epilepsy, and response to anti-seizures medications (ASMs).

Results: Fifty-one patients were included, with a median age of 9 years (range: 1 month-36 years). 39/53 had intellectual disability (ID), either severe/profound (26%), mild-moderate (56%), or global developmental delay (18%). Normal cognition was reported in 5 (10%) (data not available in 7). 23/51 (77%) had behavioral problems and/or autism.

Epilepsy was reported in 35/51 (69%), with a median age at onset of 2 years (range: 1 day–14 years); 40% had genetic generalized epilepsy (GGE), 23% severe developmental and epileptic encephalopathy (DEE), 37% unclassified epilepsy.

Seizure types included absences (51%), generalized tonic-clonic-seizure (TCS) (34%), clonic-myoclonic/hemiclonic (29%), focal (17%), tonic (23%), febrile seizures (9%), focal-to-bilateral TCS (3%). Two patients had seizures in cluster. Among epileptic patients EEG was normal in 2 (8%), and showed epileptiform discharges in 19 subjects, either generalized (47%), focal (32%), or multifocal (37%). 7/35 (20%) patients achieved seizure-freedom either in monotherapy with ETS (2), LEV (1), VPA (3) or in combination of TPM-LTG (1). Sodium Channel Blockers (SCB) induced seizure worsening in 5, and partial seizure control in 4 cases.

Patients harbored 36 different variants (12 missense, 24 truncating/frameshift); 18/36 (50%) occurred de novo.

Conclusion: We report detailed genotype-phenotype correlations in a large cohort of subject with LOF-SCN8A-diseases. Generalized epilepsy with absences, late epilepsy-onset, and poor response to SCBs seem to be the major features of LOF-SCN8A.
In vitro human model of focal cortical dysplasia demonstrates early junctional instability in the neuroepithelium and network hyperexcitability

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Purpose: One of the limitations to developing effective treatments to control seizures in patients with focal cortical dysplasia (FCD) is the lack of a reliable model that recapitulates the emergence of the condition during human neurodevelopment. Thus, to better understand the mechanism leading to FCD, we generated patient-derived cortical organoids from induced pluripotent stem cells (iPSCs).

Method: We generated forebrain cortical organoids from four patients with FCD type II and four controls, and subsequently characterized the cortical organoids at three levels: morphological, molecular, and functional. We reprogrammed skin fibroblasts into iPSCs, and performed immunofluorescence staining, deep whole-exome sequencing, target gene expression, synaptic puncta quantification, and extracellular electrophysiology.

Results: Using this human model, we mimicked some FCD hallmarks, such as impaired cell proliferation, the presence of dysmorphic neurons and balloon cells, and neuronal network hyperexcitability. Furthermore, we observed alterations in the adherens junctions’ zona occludens-1 and partitioning defective 3, reduced actin cytoskeleton polarization, and fewer synaptic puncta. FCD cortical organoids showed downregulation of the small GTPase RHO A, a finding confirmed in brain tissue resected from patients with FCD type II. Furthermore, both spontaneous and optogenetically-evoked electrical activity and enhanced network connectivity in the FCD organoids.

Conclusion: Our findings suggest a ventricular zone instability in tissue cohesion of neuroepithelial cells, leading to a maturational arrest of progenitors or newborn neurons, which may predispose to cellular and functional immaturity and compromise the formation of neural networks in FCD. This model may help to understand further the pathophysiology of FCDs and other malformations of cortical development.

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Impact of genetic testing on therapeutic decision making in childhood-onset epilepsies - a study of a tertiary referral centre

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Purpose: To assess how genetic testing enables precision therapy at a tertiary epilepsy centre.

Method: Medical records of children born between 2006 and 2011 and followed at the Danish Epilepsy Centre in 2015 were systematically analyzed. Only non-acquired epilepsies were included. Genetically unsolved patients underwent informed consent for study inclusion and genetic testing. We found a genetic diagnosis in 102 patients. Most common epilepsies were focal epilepsies, multifocal developmental and epileptic encephalopathies (DDEs) and electroclinical syndromes such as epileptic spasms and Dravet syndrome. Highest diagnostic yield was amongst those with seizure onset before the second birthday and those with early infantile DEE, Dravet syndrome, multifocal DEE and epileptic spasms. Of 102 genetically solved patients, 53 were eligible for precision therapy approaches. Treatment was adjusted in 32/53 (60%); > 50% reduction in seizure burden was reported in 30/32 (93%) while only 4/30 patients became seizure-free.

Conclusion: A genetic diagnosis is present in a large proportion of patients with primary epilepsy at a specialized epilepsy centre. Although, precision therapy only help a minority of genetically solved patients to reach seizure-freedom, reaching a genetic diagnosis enables precision therapy approaches in half of patients; a strategy that often results in > 50% reduction in seizure burden.
Delineation of the epileptic and neurodevelopmental phenotype associated with germline variants of the RORB gene


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Purpose: Several studies have demonstrated the importance of RORB gene in the nervous system in murine models contrasting with the limited knowledge concerning the impact of pathogenic variants on human neurodevelopment. The number of patients studied so far, although limited, indicate an association with intellectual disability and epilepsy. We aimed to delineate the spectrum of epileptic seizures and syndromes in a large cohort of patients harboring RORB germline variants and to assess their neurocognitive profile.

Methods: Through an international collaboration, we analyzed the phenotypes and genotypes of 30 patients with RORB variants, using an excel file with detailed item concerning medical records, intellectual status, EEG and MRI.

Results: 30 patients carrying RORB variants were studied, 28 unreported patients and 2 patients with revised data (15 male, median age, 9.5 years (range 1-21y)). Seizures were reported in 26/30 (87%) patients, with a median age at onset of 3 years (range 4 mo–12y). The most frequent epilepsy syndrome was absence epilepsy, including childhood absence epilepsy (n=6), juvenile absence epilepsy (n=1), early onset absence epilepsy (n=4), epilepsy with myoclonic absence seizures (n =3), eyelid myoclonia with absence epilepsy (n=4), myoclonic epilepsy in one patient, focal epilepsy in 2 patients, rare febrile seizure in one patient. Three individuals had genetic generalized epilepsy combining several types of seizures including tonic seizures, and one patient had continuous spike and waves during sleep. Intellectual disability was described in 25 of 30 (83%) patients, being mild in 13 patients, moderate in 10 patients, and severe in 2 patients.

Conclusion: The patients’ phenotype was characterized by generalized seizures and syndromes, particularly a large spectrum of absence seizures with mild to moderate cognitive impairment, irrespective of the expected functional effect of genetic variant. Functional studies are underway to test the consequences of certain variants in cultured neurons.
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The neonatal presentation of BRAT1-encephalopathy

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Purpose: BRAT1-encephalopathy is an ultra-rare, autosomal-recessive disorder. Due to its early-lethality, patients may die undiagnosed. We aim to provide insight for early recognition of BRAT1-encephalopathy in the neonatal period.

Methods: We analyzed the clinical, neurophysiological and neuroradiological findings of ten unrelated neonates with pathogenic variants in BRAT1 who presented in neonatal period. Neuropathology was obtained in two patients.

Results: Most newborns (9/10) presented with hypertonia and developed myoclonic jerks exacerbated by stimulation during the first three days of life, except one late-preterm neonate with onset of symptoms at 40 weeks post-menstrual age. At onset, video-EEG demonstrated a normal or mildly discontinuous background in most patients, without EEG correlate for the myoclonic jerks, 3/10 had multifocal epileptiform abnormalities but no seizures recorded. Multifocal clonic seizures appeared after a mean of 21(SD:12,13) days of life. Progressively, neonates showed acquired microcephaly, encephalopathy, and bouts of apnea and bradycardia leading to death at a mean age of 2,5(SD:1,31) months of life. Two patients died at 19 and 30 months of life. Pathogenic variants in BRAT1 gene were homozygous in 6/10 patients and heterozygous-compound in 4/10 patients, including 6 duplications, 5 deletions, and 3 missense mutations. Three patients were initially diagnosed with hyperekplexia, 6/10 were diagnosed months to years postmortem on stored DNA samples. Neuropathology revealed marked delay in myelination and severe and diffuse astrogliosis sparing the upper cortical layers.

Conclusion: Neonates with BRAT1 pathogenic variants present with congenital hypertonia and early-onset myoclonic jerks. EEG can be falsely reassuring initially, misleading to the diagnosis of hyperekplexia, but acquired microcephaly, encephalopathy, and the evolution into intractable seizures, multifocal myoclonus, apnea and bradycardia, suggest BRAT1 encephalopathy. The relative preservation of upper layer of the cortex could account for the initially normal EEG. Early diagnosis of BRAT1-encephalopathy can reduce unnecessary diagnostic procedure and provide families with genetic counseling.
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Characterization of neural dynamics between the anterior thalamus and the cortex in epilepsy patients

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Due to its connectivity profile to cortical regions and its suggested role in the subcortical propagation of seizures, the Anterior Nucleus of the Thalamus (ANT) is chosen as the stimulation target in Deep Brain Stimulation (DBS) for drug-resistant epilepsy (DRE) (Salanova V et al. Neurology 2015; 1017-1025). Here, we aimed to analyze how the ANT interacts with the neocortex and to explore the electrophysiological mechanisms underlying the effectiveness of this method.

Electroencephalograms (EEG) and ANT Local Field Potential (LFP) have been recorded in parallel during bilateral implantation of DBS leads in 12 patients. High-frequency test stimulations in the ANT have been delivered, while EEG was recorded.

The strongest interaction dynamics (wpli-debiased) between the scalp and ANT bilaterally was found in the theta band (N-way ANOVA, \( p < 0.0001 \)), with F3/F4 channels most strongly connected to left/right ANT respectively. When comparing left/right connectivity profiles, we could confirm the specificity of ANT interaction to ipsilateral centro-frontal regions, with F3/F4/C3/C4 showing statistically significant differences (paired t-test).

We analyzed EEG properties with (“ON”) and without (“OFF”) stimulation (paired t-test) in 10 patients. We found an increase in delta and high-beta \(( p<0.001 \) ) and a decrease in theta, alpha and low-beta spectral power \(( p<0.001 \) ) (ON-condition).

Scalp Global Connectivity (wpli-debiased) showed a statistically significant increase (ON-condition) in all frequency bands \(( p<0.001 \) ).

We finally explored how these measures correlated to responsiveness (reduction in seizure frequency 6 months post-implantation). Both ANT and scalp theta power correlated positively to responsiveness, and a higher Global Scalp Connectivity (in all frequency bands) in the ON condition predicted better responsiveness (Pearson’s, \( p<0.05 \)).

In conclusion, this study represents to our knowledge an unprecedented characterization of the dynamical interactions between the ANT and the cortex, providing crucial information to optimize DBS on patients eligible to intervention and to predict its success.

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Role of vagal nerve stimulation (VNS) on thalamo-cortical network: a study of somatosensory evoked potentials (SEPs) and quantitative electroencephalography (qEEG)

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Purpose: VNS is a viable choice in non-surgical cases of drug-resistant epilepsy, but its specific mechanisms of action remain still unclear. We performed a SEPs and qEEG analysis in patients with drug-resistant epilepsy with the aim of exploring neuromodulative effects of VNS on thalamo-cortical network and its clinical implications.

Methods: Eight patients, all eligible for VNS therapy (four men and four women, mean age 49.3±11.3 years old, with a history of epilepsy of 39.9±11.7 years old), were enrolled. SEPs were recorded from dominant hand both before VNS therapy (T0) and 3-6 months later (T1). We matched T0 with two paired variables: T1ON and T1OFF (VNS active and inactive mode, respectively). Contextually, all participants underwent a 35-minute recording with a high density 64-channels EEG. We analysed two qEEG parameters: IAF (Intermittent Alpha Frequency) and PSD (Power Spectrum Density) for the following spectral bands: delta, theta, alpha and beta.

Results: Only one patient could be defined seizure responder however 50% of patients reported a global satisfaction in terms of seizure’s severity and quality of life after VNS therapy. SEPs analysis showed that N20 amplitude increased from T0 to T1 both in the OFF than in the ON mode \(( p=0.004 \) and \( p=0.038 \) respectively). P24 amplitude increased both from T0 to T1OFF than when comparing T1OFF with T1ON \(( p=0.05 \) and \( p=0.048 \) respectively). PSD analysis revealed a decrease in delta and an increase in alpha power after VNS therapy, with statistical significance between T0 and T1OFF \(( p=0.040 \) ).

Conclusions: We hypothesize that these SEPs modifications are suggestive of a possible role of VNS in a chronic modulation of thalamo-cortical network which would contribute to its anti-epileptic effect. PSD changes evidenced by qEEG analysis could represent an indirect indicator of the potential role of VNS in improving patients’ cognitive performance and quality of life.
Purpose: In the recent years, epilepsy research has undergone a paradigm shift from a focal cortical disease towards the understanding of the condition as a network disease. The shift is motivated by new evidence of widespread brain activity as key factor in seizure initiation and maintenance, and by the promising results of brain stimulation for drug-resistant cases of epilepsy. However, a thorough understanding of the network-rooted epileptic dynamics is still missing, and the details of the stimulation procedures do not account for the variable brain network dynamics between patients.

Methods: We develop a method to construct personalized dynamical models of epileptic networks, based on EEG recordings in an entirely data-driven manner. A dynamic connectivity matrix, which simultaneously captures the dominant spatial and temporal modes in the epileptic network, is extracted to model the steady state EEG dynamics. The considered population includes 30 patients whose brain dynamics exhibits frequent epileptiform discharges ("active EEG"). The dynamical properties of the active and inactive EEG states are compared for each patient.

Results: Our model allows to accurately reproduce the clinically relevant properties of the recorded active EEG dynamics: spectral power, channel coherence and amplitude variation. We find the dominant coherent structures for each epileptic network state. In addition, the extracted models allow to directly simulate the effects of external network stimulation. By relying on the comparison of the two types of brain dynamics, the model is used to predict targeted interventions to transition from pathological to healthy brain dynamics.

Conclusion: We developed personalized EEG-driven models of the epileptic network dynamics. We demonstrated their accuracy for patients with active EEG dynamics. The models can be readily used to predict the optimal localization and suitable stimulation parameters of patient-specific interventions to help resolve the pathological epileptic network states.

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Laryngeal motor evoked potentials as biomarkers of Vagus Nerve Stimulation responsiveness in drug-resistant epilepsy

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Purpose: Vagus Nerve Stimulation (VNS), due to co-activation of the recurrent laryngeal branch, elicits Laryngeal Motor Evoked Potentials (LMEPs), a proven marker of afferent fiber activation. Based on LMEPs characteristics, we used Support Vector Machine (SVM) to build a classification model of VNS responsiveness in patients with drug-resistant epilepsy (DRE).

Method: We recruited DRE patients with at least 3 months of VNS therapy duration (responders=>50% seizure-frequency reduction). Trains of 14s were delivered at increasing current, up to the routine stimulation intensity (I_{stim})+0.25 mA. LMEPs were recorded by 2 skin electrodes placed horizontally on the ventral surface of the neck. LMEP latency at I_{lat} and LMEP amplitude at the plateau (Y_{plat}) were measured for all patients. We fitted the amplitude values to a stimulus-response curve (Boltzmann sigmoid function) to extract the slope (k), theoretical threshold (thr_{50}, 5% curve saturation), and intensity leading to the curve’s half-saturation (I_{sat}). Features were recursively added to build an SVM classification model, based on their discrimination power between non-responders and responders. Grid-search was used to select the model with the best classification accuracy, applying leave-one-out cross-validation.

Results: LMEPs were successfully recorded in 42/45 patients. 17 patients (9 responders, 8 non-responders) showed a successful Boltzmann fitting (R_2>0.95, 2 points on slope), and were used to build a classification model. The model leading to the best classification accuracy was trained using 5 features (thr_{50}, I_{sat}, k, Y_{plat}, latency). The best performing model led to a classification accuracy of 88.2%, a sensitivity of 88.9% and a specificity of 87.5%.

Conclusion: LMEPs are an accessible and reliable marker of effective vagal activation. Using machine learning, we built a classification model that can accurately discriminate non-responders from responders to VNS, based uniquely on peripheral nerve activation characteristics. Further stimulation steps may be needed to improve stimulus-response fitting and enable characteristics extraction in more patients.
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The analogy between structural networks obtained from diffusion weighted imaging and effective networks derived from single pulse electrical stimulation in people with epilepsy

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Purpose: Epilepsy is regarded as a network disorder. Effective networks describe the connections between brain regions by perturbation of one region e.g., by single pulse electrical stimulation (SPES). Structural networks describe the connections between brain regions via white matter tracts derived from diffusion weighted imaging (DWI). We studied the similarity between these structural and effective networks. Comparison of the presence and strength of patient-specific connections between modalities can expand our knowledge of epileptogenic networks.

Method: We included patients who underwent DWI and long-term intracranial EEG monitoring with subdural electrocorticography (ECoG) or stereoEEG (sEEG). An automatic detector was optimized to detect early responses from SPES (0.2Hz, 10 stimuli) for both ECoG and sEEG. Effective networks were constructed with electrode contacts representing the nodes. Edges were drawn from the stimulus pair to the electrodes with early responses. DWI was acquired with 62 diffusion directions (b=1600s/mm2). Anatomical constrained probabilistic fiber tractography using constrained spherical deconvolution was performed with electrode contacts as regions of interest. Structural networks were constructed by the streamline density as edge between regions of interest. We will compare both networks with the Jaccard index and graph measures (degree, betweenness centrality, clustering coefficient) in- and outside epileptogenic tissue.

Results: We included 15 patients (six ECoG, eight sEEG, one sEEG+ECoG). The SPES-detector had a sensitivity of 82% and 78% and specificity of 82% and 91% for sEEG and ECoG data respectively. The networks had 56-154 nodes per patient (median: 84). The epileptogenic zone was covered by 3-37 electrodes (median: 10).

Conclusion: We designed a method to reveal complementary network characteristics of structural and effective patient-specific brain networks for sEEG and ECoG.

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DBS of thalamic centromedian nucleus for Lennox-Gastaut syndrome (ESTEL trial)

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Purpose: Prior uncontrolled studies have reported seizure reductions following Deep Brain Stimulation (DBS) in patients with Lennox-Gastaut syndrome (LGS), but evidence from randomized controlled studies is lacking. We aimed to formally assess the efficacy and safety of DBS to the centromedian thalamic nucleus (CM) for treatment of LGS.

Methods: Prospective, double-blind, randomized study of continuous, cycling stimulation of CM-DBS, in patients with LGS. Following pre- and post-implantation periods, half received three-months stimulation (blinded phase), then all received three-months stimulation (unblinded phase). Primary outcome was the proportion of participants with ≥50% reduction in diary-recorded seizures in stimulated versus control participants, measured at the end of the blinded phase. A secondary outcome was the proportion of participants with ≥50% reduction in electrographic seizures (24-hour EEG) at the end of blinded phase. We also explored seizure frequency at study exit relative to baseline, burden of EEG interictal discharges pre- and post-stimulation, and changes in cognitive/behaviour assessments.

Results: Between November 2017-December 2019, 20 young adults with LGS (17-37 years;13 females) underwent bilateral CM-DBS at a single centre in Australia, with 19 randomized (treatment, n=10; control, n=9). 50% of the stimulation group achieved ≥50% seizure reduction, compared with 22% of controls (OR3.1; 95%C1.44-21.45; p=0.25). For electrographic seizures,89% of the stimulation group had ≥50% reduction at the end of the blinded phase,compared with none of the controls (OR23.25; 95%C1.0-538.4; p=0.05). Across all patients, median seizure reduction (baseline vs study exit) was 46.7% (IQR:28-67%) for diary-recorded seizures and 53.8% (IQR:27-73%) for electrographic seizures. No changes were observed in epilepsy disability/severity/functional ability scores after three-months of stimulation.

Conclusion: CM-DBS in patients with LGS reduced electrographic rather than diary-recorded seizures, after three-months of stimulation. 50% of all participants had diary-recorded seizures reduced by half at study exit, providing supporting evidence of treatment effect.

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Discrepancy between subjective and objective memory change after epilepsy surgery and relation with quality of life

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Purpose: Complaints pertaining to memory functioning are among the most often reported cognitive symptoms in patients with epilepsy. However, research suggests a considerable mismatch between patients' perception of memory functioning and the objective performance as measured with standardized neuropsychological tests. Depressive mood might be an important factor in explaining this discrepancy. As a new approach, the present study aimed to quantify the mismatch between subjective and objective memory functioning by considering the dynamic change of these factors as well as depressive symptoms after epilepsy surgery. Moreover, their influence on the overall quality of life was investigated.

Method: Pre- and postoperative (24 months) data from 78 patients with focal epilepsy (28% extratemporal) were retrospectively analyzed. Data from standard neuropsychological assessment included verbal memory capacity and self-ratings of subjective memory, depressive symptoms, as well as quality of life.

Results: The results showed that (1) patients with clinically relevant postoperative depressive symptoms underestimate their actual memory performance; (2) the relationship between objective memory change and quality of life is mediated by the factors subjective memory change and depressive mood.

Conclusion: Our data demonstrate a quantitative approximation of a pronounced depression-related negative bias in self-perception of memory functioning of roughly 1 to 1.5 standard deviations. At the same time, our data indicate that patients' perceptions of memory functioning can be quite accurate in the absence of depressive symptoms. Additionally, subjective perception of memory performance and depressive mood may critically determine if objective memory changes contribute to patients' postoperative QoL. Taken together, our study highlights the clinical relevance of incorporating subjective measures of memory functioning and mood that go beyond objective memory performance for the interpretation of how changes in memory functioning may affect patients' quality of life after epilepsy surgery.

Machine learning applications to differentiate comorbid functional seizures and epilepsy from pure functional seizures

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Purpose: We have utilized different methods in machine learning (ML) to develop the best algorithm to differentiate comorbid functional seizures (FS) and epilepsy from those who have pure FS.

Methods: This was a retrospective study of an electronic database of patients with seizures. All patients with a diagnosis of FS (with or without comorbid epilepsy) were studied at the outpatient epilepsy clinic at Shiraz University of Medical Sciences, Shiraz, Iran, from 2008 until 2021. We arbitrarily selected 14 features that are important in making the diagnosis of patients with seizures and also are easily obtainable during history taking. Pytorch and Scikit-learn packages were used to construct various models including random forest classifier, decision tree classifier, support vector classifier, k-nearest neighbor, and TabNet classifier.

Results: Three hundred and two patients had FS (82.5%), while 64 patients had FS and comorbid epilepsy (17.5%). The “TabNet classifier” could provide the best sensitivity (90%) and specificity (74%) measures (accuracy of 76%) to help differentiate patients with FS from those with FS and comorbid epilepsy.

Conclusion: These satisfactory differentiating measures suggest that the current algorithm could be used in clinical practice to help with the difficult task of distinguishing patients with FS from those with FS and comorbid epilepsy. Based on the results of the current study, we have developed an Application (SeiDx). This App is freely accessible at the following address: https://drive.google.com/file/d/1rAgBXKNPW9bmUCDiOaGHHzLBQgzZ-HZ2/view. This App should be validated in a prospective assessment.
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**Ictal SPECT in psychogenic non epileptic seizures (PNES). Identification of functional brain networks involved in PNES**

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**Purpose:** Psychogenic non-epileptic seizures (PNES) are part of the functional conversion disorders. The neurobiological mechanisms underlying these disorders remains poorly understood. Recent research in this field is focusing on establishing neurobiological models to explain this disorder. It has been hypothesized that brain regions involved in the perception of external and internal stimuli (such as autonomic body changes), attention networks and networks involved in “self agency” may be implicated in the generation for PNES. Functional imaging such as ictal brain single-photon emission computed tomography (SPECT) can provide valuable information to characterize functional networks related to the generation PNES. The purpose of this study is to characterize de brain regions involved in the episodes of PNES using Ictal and Interictal SPECT.

**Method:** Nineteen patients in whom Ictal SPECT was obtained during an episode of PNES while admitted in the video EEG monitoring unit were retrospectively reviewed.

Ictal SPECTS were subtracted from the interictal SPECT to generate SISCOM (Subtraction of Ictal SPECT co-registered to MRI) images.

Group analysis of the SISCOM images was conducted in order to identify common regions of activation and deactivation during the PNES episode across the group of patients. Whole brain analysis, as well as hypothesis based analysis on networks of interest of was performed using SPM.

**Results:** During the PNES there was increased activity in the medial prefrontal cortex, motor regions, anterior insula and basal ganglia, corresponding to regions involved in the perception of autonomic changes, sensory perception, motor control as well as attention networks. Conversely there was a reduced activity in the temporo-parieto-occipital junction bilaterally likely implying inhibition of areas associated to self-agency processes.

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**Temporal trend of increasingly later age at onset of mesial temporal lobe epilepsies between 1997 and 2018 suggests changing etiologies with distinct neuropsychological features**

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**Purpose:** Research in the context of temporal lobe epilepsy surgery suggests temporal trends of changing patient populations with a decreasing number of patients with classic early onset mesial epilepsy with hippocampal sclerosis (mTLE). At the same time neuropsychologists discuss “neuropsychological phenotypes” in TLE as defined by distinct impairment patterns. The present study aims at the connection of both trends.

**Method:** Anonymized data sets of a cohort of 1059 patients with the diagnosis of mTLE, collected monocentric between 1997 and 2017/18, were retrospectively evaluated in regard to temporal trends of age at epilepsy onset, neuropsychological performance, and suggested MRI pathology. Different from our multicenter study in 2014 (Eur J Neurol. 2014 Jun;21(6):827-34), we now included patients with early and late onsets of epilepsy.

**Results:** First we could replicate our finding of an increasing age at epilepsy onset from 2014 (1997-2003: m=12±11 years vs. 2014-2018: m=28±18 years; F=45.1(3), p<0.001). Bilateral MRI pathologies increased (1997-2003: 7.8% vs. 2014-2018: 25%, chi2(6) =36, p<0.001). Performance in IQ, motor, executive and verbal memory functions appeared less impaired over time, and verbal/figural memory impairment patterns appeared to discriminate increasingly less between left vs. right mTLE. Notably, patients with early onset mTLE with hippocampal sclerosis (n=862) were less frequently seen over time while the number of patients with late onset mTLE suspicious of limbic encephalitis (n=197) steadily increased (1997-2003: 1.4% vs. 2014-2018: 42%, chi2(3) =160, p<0.001).

**Conclusion:** Altering clinical and neuropsychological features of mTLE patients suggest changing etiologies of mTLE over the past 20 years. Overlapping frequency distributions of patients with early onset mTLE and patients with late onset suspected limbic encephalitis explain the impression that mTLE increasingly starts later in life. Different etiologies confounded with a different age at epilepsy come along with changing neuropsychological features which may appear as distinct neuropsychological phenotypes.
Lesion extent negatively impacts cognitive functioning in pediatric focal epilepsy

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Objective: Cognitive development in children and adolescents with focal lesional epilepsy is determined by the underlying epileptogenic lesion, in addition to the seizure disorder itself. However, the distinct impact of lesion extent, lateralization, localization, and etiology on cognitive development remains largely unexplored. Here, we aimed to determine the effect of lesion-related predictors and define their interrelation with epilepsy-related predictors of cognitive development in pediatric focal lesions epilepsy.

Methods: We retrospectively analyzed the clinical data of consecutive children and adolescents with lesional epilepsy who underwent standardized cognitive or developmental evaluation yielding intelligence quotient or developmental quotient (IQ/DQ) in our institution in 2013-2021.

Results: We included 50 patients aged 0.5-17.5 years (mean, 9.3 years; SD, 4.9 years) at the evaluation of cognitive development. Epilepsy duration was 0-15.5 years (mean, 3.8 years; SD, 4.1 years). 30 (60%) patients had unilobar, 7 (14%) multilobar, 10 (20%) hemispheric, and three bilateral lesions. Etiology was congenital in 32 (64%) cases, including 19 cases with malformations of cortical development and 11 with low-grade tumors, acquired in 14 (28%) cases, and progressive in 4 (8%) cases. Cognitive development was impaired in 30% patients. For patients with unilobar lesions, mean IQ/DQ was 96.7 ± 15.8, for multilobar lesions 98.8 ± 20.1, for hemispheric lesions 78.7 ± 21.3, and for bilateral lesions 76.3 ± 4.5. Larger lesion extent and longer epilepsy duration – but not younger age at epilepsy onset, higher seizure frequency or left-sided lesions – correlated with lower cognitive functioning in univariate analysis, both contributing to the explanatory model in the multivariate analysis.

Significance: Our study demonstrates that the extent of affected brain tissue may significantly impact developmental trajectories by limiting the available resources. Longer epilepsy duration contributes to cognitive impairment and merits attention as the only modifiable predictor of cognitive outcome in pediatric focal lesional epilepsy.

Seizure duration and postictal perfusion in a human seizure model

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Purpose: The postictal state is a largely underexplored phenomenon due to the unpredictability of seizures and the concomitant inherent practical challenges to investigate it. It was recently hypothesized that the postictal state may result from hypoperfusion as a consequence from seizure-triggered vasoconstriction (Farrell J et al. eLife 2016;5:e19352). Here, we explore this hypothesis in a human seizure model, using data from patients with major depressive disorder treated with electroconvulsive therapy (ECT). We recently argued that the seizures and the postictal state in these patients have similar characteristics as observed in patients with epilepsy (Pottkämper J et al. Epilepsia Open 2021;6:672-684).

Method: We recorded 19-channel EEG in patients with a major depressive disorder treated with ECT. Seizure duration was estimated from the ictal EEG. Arterial spin labelling magnetic resonance imaging (ASL-MRI) one hour after ECT was used to quantify global postictal cerebral blood flow (CBF). Per patient, one postictal CBF-map was compared to a baseline CBF-map acquired before the ECT course to investigate perfusion changes. A linear regression model examined the predictive value of seizure duration on postictal cerebral blood flow. Data were part of a prospective, three conditions cross-over trial, with randomized condition allocation, open-label treatment, and blinded end-point evaluation (NL68690.091.18).

Results: Twenty-one patients were included. In this preliminary analysis, we found decreased postictal perfusion in the bilateral inferior and middle temporal gyrus, bilateral frontal pole, and the right angular gyrus. Seizure duration was variable (M = 63.35, SD = 28.85) and was not associated with postictal cerebral blood flow.

Conclusion: Local cerebral blood flow decreases persist one hour after seizures in ECT patients. Our findings support the postictal hypoperfusion hypothesis introduced by Farrell et al. Longer seizures were not associated with postictal cerebral blood flow changes.

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Posters by category
Adult Epileptology

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First seizure as an atypical manifestation of meningeal uve syndrome

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Purpose: Vogt-Konayagi-Harada syndrome or meningeal uve syndrome is considered as a granulomatous inflammation of multiple organs, apparatus and systems, whose pathogenic mechanisms have not been fully elucidated.

Method: 34-year-old male, disease began 7 days prior to admission when he presented Holocranial headache with intensity 7/10 which partially subsided with analgesics accompanied by bilateral tinnitus, later presence of generalized tonic-clonic movements on multiple occasions with duration longer than 5 minutes which were initially accompanied by recovery of the state of consciousness but in the last hour he does not regain consciousness so he is brought to this center. Physical Examination, he was hemodynamically stable with clinical signs of vitiligo, alopecia, uveitis with exudative retinal detachment. Additionally, generalized tonic-clonic seizures occurred.

Results: Our patient had the 5 elements for the diagnosis of this condition, since he had no history of trauma or previous ocular surgery, no findings of previous ocular disease, ocular involvement characterized by bilateral anterior uveitis with multifocal exudative retinal detachment, signs meningeal with cerebrospinal fluid pleocytosis and previous auditory symptoms and finally the dermatological findings of alopecia and vitiligo.

Conclusion: This particular case is the first report of a complete form of this condition in Venezuela and in turn one of the few descriptions in the literature where neurological and imaging manifestations consistent with demyelination of the central nervous system are appreciated. The patient finally died despite the management instituted.

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Relapse risk in new onset epilepsy

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Purpose: It has been suggested that patients presenting a first epileptic seizure benefit from swift intervention. In this large retrospective study including a comprehensive workup starting in the emergency department (ED), we investigated if introducing an antiseizure medication (ASM) already in the ED protects patients against relapses.

Method: 1011 adult patients (≥ 16 years) presenting symptoms compatible with a first epileptic seizure were enrolled. The work-up included a 2-years follow-up, brain imaging (CT or MRI), a routine and/or long-term overnight EEG, as well as specialized consultation (e.g. cardiologist) whenever necessary. Statistics included Chi-squared, t-tests, log-rank tests associated to Kaplan-Meier curves as well as logistic regressions.

Results: 241 patients experienced a relapse, most of them with a final diagnosis of new onset epilepsy (NOE; N=162/487, 33%). In NOE patients who relapsed, the median delay until the final diagnosis was shorter for the seizure-free patients group (median: 24.6 days ± 92 VS 66.5 ± 157; p=0.002). In 64 (39%) relapses occurred while treatment was slowly introduced. In 29 patients (18%) we noted poor compliance as major cause of relapse. It was associated with male sex (p = 0.02) and younger age (p = 0.012). In 25 patients (15.4%, 5% of all NOE patients), pharmacoresistance against the first drug was diagnosed. In 27%, no treatment has been introduced due to diagnostic uncertainty.

Conclusion: Our analysis of relapse in NOE suggested that most causes (66%) are iatrogenic (i.e. slow titration, or watch-and-wait-attitude). Pharmacoresistance is seen rarely in NOE. Our results support the importance of thorough work-up including prompt blood drug levels. More drugs allowing fast up-titration are needed for NOE patients in the ED.
Mental clarity induced by electrical stimulation of the dorsal anterior insula

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Purpose: This study addressed the question of the possibility of observing an ecstatic aura through the electrical stimulation of the dorsal anterior insula in epileptic patients who had never experienced ecstatic seizures, and hence with no underlying brain network changes related to a pre-existing ecstatic epilepsy.

Method: In the context of invasive presurgical evaluation of drug-resistant epilepsy, we performed electrical stimulations in the dorsal anterior insula in six patients with the specific question of reporting any mental or emotional change in addition to physical sensations. 50 Hz-bipolar stimulations (pulse width 1 msec, 3 second-duration) were performed with current intensities from 0.5 mA to 6mA. The patients were blinded to the timing of individual stimulation trains.

Results: In a 51 year-old male with a left hippocampal sclerosis and seizures including a thoracic oppression, an impairment of awareness, oro-alimentary automatisms, and bilateral hypermotor signs, an ecstatic experience was induced through electrical stimulation at 2.7 to 3 mA of adjacent contacts of an electrode located in the dorsal anterior insula. Several stimulations reproducibly induced a blissful sensation of mental clarity, without epileptiform afterdischarge on the SEEG.

Conclusion: By transiently interrupting the normal function of the anterior insular cortex by means of electrical stimulation, we could reliably reproduce ecstatic auras in one patient who had never experienced ecstatic seizures. Our findings show that the anterior insula may modulate higher cognitive functions, and play a major role in the access to a state of mental clarity. This supports our previous hypothesis that the epileptic discharge may interrupt the functional role of the anterior insula, which is to evaluate the potential conflict between interoceptive stimuli and top-down predictions, and relay surprise in case of mismatch; this interference with anterior insula may suppress signals of surprise, and hence provides a feeling of “all is under control”.

Psychogenic non epileptic seizures: are they a freeze reaction?

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Psychogenic non-epileptic seizures (PNES) clinically resemble epileptic seizures (ES) but lack epileptic activity at the time of the seizure and are also not due to any other physiological disorder. The integrative cognitive model (ICM) suggests that PNES is an automatic reaction generated from distorted memory and is perceived as uncontrollable and unwanted. Furthermore, the ICM model implies that a PNES event occurs due to an external or internal cue. Intrigued by this assumption, we wanted to examine why a PNES event occurs at a particular moment. Are there any triggers and circadian periodicity?

This study is a retrospective study. We included all patients diagnosed with PNES or ES admitted to our long-term video EEG monitoring unit (LTVEM) between 01/01/2018 and 30/08/2020. Using thorough video analysis, we checked the patient’s state at the onset of the event and looked back to see what was the patient doing before the event onset.

Thirty patients with PNES and 30 patients with ES were included in the final analysis. In 34 of 46 seizures in the PNES group, 74%, and 25 of 30 patients with PNES, 83%, preceding behavior was recorded. In contrast, a preceding behavior was observed in only one of 56 ES recorded. The preceding behavior consisted mainly of inactivity.

Patients with PNES have a preceding behavior before most PNES events with motor manifestations. Since the preceding behavior consists mainly of inactivity, we believe it may imply that PNES represents a freeze reaction.
Intention-to-use and constraints of a seizure detection device. What patients with drug-resistant epilepsy say

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Purpose: Seizure detection using heart rate variability and movement analysis, from a detailed analysis by deep learning analysis system, could help patients cope with their epilepsy. AURA Healthcare and Institut La Teppe are jointly developing a device consisting of a patch connected to a mobile application using this technology, which will help to manage seizures (automated seizure detection and evaluation of the temporal organisation in the occurrence of seizures). This exploratory study aims to identify patients’ representation of their disease and the acceptability of the technology reported following a video presentation.

Methods: 18 patients with drug-resistant epilepsy (6 women, 12 men; mean age = 38 years) were shown a video describing how the technological device works. A qualitative approach using semi-structured interviews was then used to gain an in-depth and contextual understanding of the perspectives of the patients. Data collection was followed by an iterative thematic analysis approach. An independent analysis and double coding of themes and subthemes were performe, followed by a consensus synthesis of the result, following the analysis of points of convergence and divergence.

Results: The intention-to-use was related to the possibility of being safe in case of a seizure, to warn relatives, to facilitate the medical follow-up and to advance research on epilepsy. The constraints of use were related to the waterproofness, the difficulty to monitor the alerts and the battery level, the health risks particularly associated with the device, the complexity of the interface and its insufficient discretion.

Conclusions: Consideration of the determinants of intention-to-use and assumed constraints on the development of a technology solution for patients with epilepsy is essential. These factors can be particularly useful to evolve the development process, but also to facilitate the integration of the device into care practices and, consequently, to facilitate its long-term use.

Treatment outcome following the transition to adult epilepsy care in childhood-onset epilepsy

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Introduction: Transition from pediatric to adult epilepsy care in patients with childhood-onset epilepsy can be challenging, and several aspects should be considered, including comorbidities, achieving social milestones, and adjustment of anti-seizure medications (ASMs). However, there is limited information regarding the treatment outcome following the transition to adult epilepsy care in childhood-onset epilepsy.

Materials and methods: We performed a 13-year retrospective study of patients with childhood-onset epilepsy who had been transferred to our adult epilepsy clinic. Treatment outcomes were divided into two groups: seizure improvement (at least 50% reduction of seizure) and stationary or worsening seizures.

Results: Among the 2,365 patients in our epilepsy cohort, 140 with childhood-onset epilepsy were transferred to our adult epilepsy clinic. Treatment outcomes were divided into two groups: seizure improvement (at least 50% reduction of seizure) and stationary or worsening seizures.

Conclusion: Our study shows that one-third of patients having childhood-onset epilepsy can experience seizure improvement following transition to adult epilepsy care, and the presence of epileptiform discharges on EEG may not necessarily mean a poor prognosis or drug-resistant epilepsy following the transition.
Improper behavior with nose-drill und laughter: gelastic seizures (GS) outside hypothalamus in adults

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Purpose: Gelastic seizures (GS) are a rare form of epileptic seizures characterized by inappropriate forceful laughter and recognized as a hallmark for the hypothalamic hamartomas. We present a rare case with GS, which was misdiagnosed as behavioral disturbance.

Methods: The 23-years-old left-handed patient was referred because of episodic behavioral disorder. He was born in the 32nd pregnancy week and suffered from a shunt-obligated obstructive hydrocephalus resulted by a perinatal cerebral periventricular bleeding. After a relatively normal development were nocturnal epileptic seizures with staring, automotor symptoms of the right side followed by generalized tonic-clonic seizures in 2012 observed without abnormality in several scalp-20-minutes-EEGs. An adjunctive therapy with Levetiracetam and Oxcarbazepin achieved a seizure freedom for 2 years. Since 2016 he unconsciously showed inappropriate episodes with nose-drill and uncontrolled laughter without abnormality in various EEG-diagnoses.

Results: During our video-EEG-monitoring (10/20+temporobasal electrodes F11/F12, FT9/FT10, TP9/TP10) several episodes were recorded during wakefulness as well as in drowsiness for maximal 53-seconds recorded. Without aura the patient gazed to the left side by impaired consciousness, showed nose-drill with his left hand then forceful laughter by dystonia in the face and tongue. After an abrupt end he regained his consciousness but with motoric aphasis. The ictal scalp EEG suggested a seizure origin in the right frontocentrobasal region with prompt propagation to bilateral frontotemporobasal. Therefore GS with a seizure origin in the right frontal lobe could be diagnosed. The cMRT showed gliosis in the right frontal lobe along the penetration channel of the VP-shunt without abnormality in hypothalamus and the whole temporal lobe.

Conclusions: GS could also be generated by other cortical area besides hypothalamic hamartomas. In such cases video-EEG-monitoring plays an essential role of the differential diagnosis. The combination of stereotypical ictal unilateral automotor “nose drill” with laughter could be a lateralizing sign.

Knowledge about SUDEP: from fear to the reality. What people with epilepsy and families in Brazil think about counseling: when, who, how and what might change after information?

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Purpose: Sudden unexpected death in epilepsy (SUDEP) is the second leading cause of death in people with epilepsy (PWE), affecting 12% of those with drug resistant seizures. The concept that SUDEP counseling would cause fear, anxiety and finally not change outcome evolved due to recognition of effective prevention measures. Nevertheless, worldwide awareness is still insufficient. The objective was to assess the knowledge, preferences and attitudes of PWE, family members and caregivers (FC) about SUDEP in Brazil.

Method: An online questionnaire approved by ethics committee was available on social media of Brazilian Epilepsy Association.

Results: 533 complete questionnaires (311 PWE; 222 by FC on behalf of patients), median age 33.5 (+9.64) and 18.8 (+15.03) years, respectively, most female (84.9% PWE; 57.2% FC). Mental/intellectual or physical disability was declared by 15% (PWE) and 32.4% (FC), active seizures by 61.1% and 71.6%, and polytherapy by 49.8% and 64.4%. Tonic clonic seizures were reported in the last 12 months by 56.9% and 81.7%. 48.6% PWE and 61.3% FC heard about SUDEP, rarely by clinicians (11.3% and 16.2%). No counseling by physicians were available in 89.6% and 76.4%, despite most wanted to know (76.5% and 77.9%) close to diagnosis. Most PWE and FC (96%) reported that they would change behaviors after being informed about SUDEP risk such as accepting devices to detect seizures, treatment and lifestyle changes and better adherence to them. Fear and sadness were the most common reported feelings, but despite that, >80% responders believed that counseling should be done to all.

Conclusion: PWE and FC in Brazil want to know about SUDEP by the physician. They consider that treatment and behavior changes would potentially be used to prevent this issue. The results are similar to those found in other countries, despite different religious and cultural backgrounds.
The association of early epileptic seizures after ischaemic stroke with impact on stroke outcome and occurrence of late seizures

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Purpose: To determine the association of early epileptic seizures (ES) after ischaemic stroke with impact on stroke outcome and occurrence of late ES.

Methods: 166 patients, treated for ischaemic stroke in the Hospital of Lithuanian University of Health Sciences Kaunas Clinics, were enrolled in a prospective cohort study. Initially, data about early ES (≤14 days) were collected, followed by an observation period of 1 year for the occurrence of late ES and evaluation of functional independence using the modified Rankin Scale.

Results: Early ES occurred in 11(6.6%) participants: around 50% – during the first day after stroke, 75% - during the first two days, all ES occurred during the first four days. More than half of early ES cases occurred during the first hour after ischaemic stroke. Late ES occurred in 8(4.8%) participants: 25% – during the first month, all ES occurred during the first 7 months. Participants who developed early ES had a higher probability of developing late ES (Log Rank=5.093; p<0.05). Late ES occurred in 2(18.2%) participants with early ES (n=11) and in 6(3.9%) without early ES (n=155)(p<0.05). Late ES occurred in 2(18.2%) participants without antiseizure medication treatment after early ES (n=11). No patients developed late ES if prescribed antiseizure medication after early ES. The probability of survival after ischaemic stroke was the same for participants with or without early ES (Log Rank=2.413; p>0.05). Death occurred in 1 participant (9.1%) with early ES (n=11) and 3(1.9%) participants without early ES (n=155)(p>0.05). Functional independence did not differ between participants with or without early ES (p>0.05).

Conclusion: Early ES occurred in minority of patients with ischaemic stroke. Participants who developed early ES had a higher probability of developing late ES. There was no difference in functional independence and death rate during the first year after ischaemic stroke between patients with or without early ES.

Unusual seizure trigger: seizure triggered by eating

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Introduction: A reflex seizure is a seizure triggered by specific afferent stimuli or specific activity. Reflex epilepsy is a syndrome where epileptic seizure is triggered regularly by somatosensory, visceral, visual, auditory, gustatory, olfactory, or cognitive stimuli. Eating epilepsy is a rare form of reflex epilepsy with a prevalence of 0.1-0.05% in the epileptic population.

Purpose: The purpose of this case series is to report unusual food triggering an epileptic seizure.

Method: We report 4 cases of different food trigger epileptic seizures in patients with focal epilepsy from an epilepsy unit of King Abdullah Medical City in Makkah.

Results: All four cases had seizures triggered by a specific type of food together with another non-specific trigger like lack of sleep. 2 cases had their seizure triggered by eating banana, one with eating a specific type of noodles and one patient has seizure triggered by lemon. All patients developed clusters of seizures on the day they ate the specific food. All of the four cases had focal epilepsy. Three cases with temporal lobe seizures and one had frontal lobe epilepsy. All are refractory epilepsy on multiple medications.

Conclusion: Eating is a rare under-recognized seizure trigger. Recognizing the specific type of trigger has an important role in management. Hence avoiding the specific trigger will help in better seizure control among those patients.
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Retrospective case series of seizures in systemic lupus erythematosus patients

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Purpose: Seizure, a severe form of neuropsychiatric manifestation of systemic lupus erythematosus (SLE), is to be characterized based on the disease activity of SLE and the outcomes of seizure.

Method: Consecutive patients in a tertiary hospital who presented a seizure at or after diagnosis of SLE from 2019 to 2021 were retrospectively enrolled. Patients with previous diagnosis of epilepsy were excluded. The medical records were reviewed on the demographics, types of seizure, electroencephalography (EEG), brain image findings, and the disease activity of SLE.

Results: Sixteen patients who presented seizure at or after the diagnosis of SLE were identified. All patients were female. The mean age at the time of seizure onset was 34 years (range 13 to 64 years) while the mean age at the SLE diagnosis was 27 years (range 13 to 64 years). The average time-to-seizure onset was 7.6 years (range 0 to 40 years).

There were five patients who presented generalized tonic or tonic-clonic type seizure; three patients showed focal behavior arrest, two showed unknown onset motor seizure, and two showed focal motor seizure. Thirteen patients recorded EEG. There were three patients with focal epileptic activity, three with diffuse anomalies, three with both focal and diffuse anomalies, and three with normal EEG activity. Fifteen patients received antiepileptic drugs. Three out of fifteen are seizure-free state for more than 5 years.

Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), a global index of a clinical index for the disease activity in SLE for the last 10 years, was extracted from the medical records. The mean value of the recent SLEDAI scored was 3.

Conclusions: While there is no consensus made on treatment of seizure occurred in SLE, it is important to promptly characterize seizures in SLE for the better outcome in the course of SLE.

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Spectral power of interictal EEG in epilepsy and functional non-epileptic seizures

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Purpose: Abnormalities in alpha rhythm have been demonstrated in people with epileptic seizures (ES). Such quantitative parameters derived from resting-state electroencephalogram (EEG) may provide useful information, but little is known about how these compare to people with functional non-epileptic seizures (FS), which are a common differential diagnosis. The purpose of this study was to investigate differences in frequency-based resting-state EEG measures in ES and FS groups.

Methods: We identified patients with a video-EEG confirmed diagnosis of FS (n=26) or ES (n=26). All patients had undergone previous routine clinical EEG study on which this analysis was performed. After pre-processing, spectral power was computed from 20-second EEG segments during eyes-closed wakefulness, prior to activation procedures and free from interictal abnormalities. Power was quantified in high- (10-11 Hz) and low-alpha (6-9 Hz) bands. Alpha-power shift was calculated by dividing low-alpha power by high-alpha power in each epoch. Peak alpha frequency was extracted from each EEG power spectrum. The analysis was repeated using a second 20-second epoch as a control analysis. Mann-Whitney-U test was used to compare groups.

Results: Compared to those with FS, the ES group had lower high-alpha power (p=0.023, rank-biserial correlation rB=0.367) and greater alpha-power shift (p=0.035, rB=0.340). Although there were no statistically significant differences in the low-alpha power, the ES group had a higher low-alpha power compared to those with FS. Peak alpha frequency was lower in ES compared to FS but did not reach statistical significance (p=0.09, rB=0.274). These findings were replicated in the second control analysis (high-alpha power p=0.034; alpha-power shift p=0.037). Age did not differ significantly between groups.

Conclusion: EEG spectral power changes in the high-alpha band differed significantly between ES and FS groups, providing evidence for alpha slowing in ES compared to FS. This may reflect a degree of cortico-thalamic dysfunction in ES compared to FS.
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Impact of number of lifetime antiseizure medications on 12-month effectiveness, quality of life and tolerability outcomes of adjunctive brivaracetam in patients with focal seizures: post-hoc analysis of a real-world European study

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Purpose: To analyse the impact of number of lifetime antiseizure medications (ASMs) on effectiveness (retention, seizure freedom), quality of life (QoL), and tolerability of adjunctive brivaracetam (BRV) in the real-world clinical routine setting in patients aged ≥16 years with focal seizures.

Method: Patients received up to 12-month adjunctive BRV treatment per clinical practice in a post-marketing, prospective, non-interventional European study (EP0077; NCT02687711). Post-hoc analyses were performed on subgroups of patients by number of lifetime ASMs (0-3, 4-6, and ≥7).

Results: Of 541 patients (full analysis set), 127 (23.5%), 141 (26.1%), and 273 (50.5%) had 0-3, 4-6, and ≥7 lifetime ASMs, respectively. At baseline, the median number of focal seizures/28 days was 1.33, 2.67, and 6.67 in patients with 0-3, 4-6, and ≥7 lifetime ASMs, respectively. At 12 months, BRV retention was 66.9%, 59.6%, and 52.4% in patients with 0-3, 4-6, and ≥7 lifetime ASMs, respectively. At 12 months, BRV retention was 66.9%, 59.6%, and 52.4% in patients with 0-3, 4-6, and ≥7 lifetime ASMs, respectively; and 29.3%, 13.6%, and 4.7% of patients were seizure free.

Clinically meaningful improvement from baseline in QOLIE-31-P total score was reported in 60.0%, 39.5%, 45.0% of patients with 0-3, 4-6, and ≥7 lifetime ASMs, respectively. Most patients improved in Clinical Global Impression of Change (76.3%, 73.9%, and 60.3% in patients with 0-3, 4-6, and ≥7 lifetime ASMs, respectively; and 29.3%, 13.6%, and 4.7% of patients were seizure free. Clinically meaningful improvement from baseline in QOLIE-31-P total score was reported in 60.0%, 39.5%, 45.0% of patients with 0-3, 4-6, and ≥7 lifetime ASMs, respectively. Most patients improved in Clinical Global Impression of Change (76.3%, 73.9%, and 60.3% in patients with 0-3, 4-6, and ≥7 lifetime ASMs, respectively; and 29.3%, 13.6%, and 4.7% of patients were seizure free. Clinically meaningful improvement from baseline in QOLIE-31-P total score was reported in 60.0%, 39.5%, 45.0% of patients with 0-3, 4-6, and ≥7 lifetime ASMs, respectively. Most patients improved in Clinical Global Impression of Change (76.3%, 73.9%, and 60.3% in patients with 0-3, 4-6, and ≥7 lifetime ASMs, respectively; and 29.3%, 13.6%, and 4.7% of patients were seizure free.

Conclusion: This post-hoc analysis of a European real-world study showed that patients with fewer lifetime ASMs before BRV initiation had higher retention and seizure-freedom rates, improvement in QoL, and lower incidences of TEAEs on BRV. Patients with ≥7 lifetime ASMs could also benefit from BRV treatment, as shown by 12-month retention and improvements in QoL.

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Epilepsy and COVID-19 infection

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Purpose: The aim is to show new-onset epilepsy and seizure relapse as a neurological manifestation of COVID-19 infection and EEG usefulness to diagnose non-convulsive epileptic status.

Methods: Five patients on the age of 18 - 54 years, were evaluated clinically, with laboratory, EEG, imaging, and neuropsychological methods.

Results: New-onset epilepsy during COVID-19 was diagnosed in three, seizure relapses in two patients. A 33-year-old male had his first GTCS during acute COVID-19 infection, assumed to be an acute seizure, no ASM was started. One month later a second GTCS happened, and 2 more in the next months during ASM titration. An 18-year-old male had his second GTCS during the covid-19 infection. EEG showed generalized poly-spike-wave discharges, MRI was normal and GGE was diagnosed. His first GTCS has happened a month ago with normal laboratory and EEG findings. The 22-year-old female started to manifest left-sided motor facio-brachial dystonic seizures (FBDS) with impaired awareness, a month and a half prior she has been diagnosed with asymptomatic covid-19 infection finding specific covid-19 antibodies. FBDS were rare in the beginning, treated only with diazepam, they became more frequent and as left-sided FBDS epileptic status, not responding to ASM. EEG, MR, and neuropsychological evaluation were normal. Autoimmune etiology was suspected although available testing for LGI1 and CAS antibodies were negative. Therapy with corticosteroids and immunoglobulins had favorable seizure reduction. A 54-year-old female with a history of non-convulsive epileptic status during acute infection manifested delirium during covid-19 infection. After EEG diagnosis of focal non-convulsive epileptic status and appropriate ASM treatment, the patient recovered completely. Seizure control was disrupted after 3 years in a 20-year-old male with epilepsy and autistic spectrum disorder during covid-19 infection.

Advanced behavioral age based on smartphone interactions in people with epilepsy

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Purpose: Smartphone behavior offers a unique opportunity to analyze complex behavioral patterns, accompanying healthy aging. Deviations from these patterns may provide new insights in various diseases. In this study we compared smartphone interactions of epilepsy patients with a model of aging in healthy controls.

Method: Smartphone interactions of a healthy control group (N=609, aged 16-86 years) were analyzed using a decision tree regression model to estimate chronological age based on touchscreen interactions. Smartphone interactions were accumulated over a total of 6 months and about 250 million smartphone interactions were analyzed. The interactions were clustered according to their next interval dynamics to quantify diverse smartphone behaviors ranging from a few milliseconds to a minute. This model well estimated chronological age (mean error = 0 years, mean absolute error = 6 years, R² = 0.8) and was then deployed on the smartphone interaction data of a group of people with refractory epilepsy (N=52, aged 20-70 years, median follow-up duration 160 days).

Results: People with epilepsy exhibited advanced aging of +9.15 years on average, ranging from -11 to +40.5. Advanced aging was shown across the entire age range. Further analyses into the possible determinants of advanced aging in people with epilepsy (e.g. load of antiseizure medications, epilepsy durations, seizure burden and type) are still ongoing.

Conclusion: Smartphone interactions can be used to reliably estimate chronological age. Smartphone analysis revealed that aging may be more advanced in people with epilepsy. The exact factors that contribute to this advanced aging are still being analyzed, but can give more insight into this phenomenon.

Cause-specific mortality after epilepsy surgery: a retrospective cohort study of tertiary epilepsy center

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Purpose: To determine mortality of drug-resistant epilepsy patients after surgical treatment over a 25-year period.

Methods: Medical record audit on all adult patients was performed retrospectively at the comprehensive epilepsy clinic of the Department of Neurology, Medical University of Vienna, Austria, who underwent epilepsy surgery between 1/1993 and 12/2018. Brain tumor cases or patients with only invasive recordings, where no surgery was done, were excluded. Database was linked to national death registry of Statistics Austria assessing demographic and clinical information, death certificates and postmortem examination reports. Causes of death were classified as 1) epilepsy-related, 2) natural or nonnatural causes not obviously epilepsy-related and 3) unknown. Study was approved by local Ethics Committee.

Results: 578 patients (291 female, 51%) underwent epilepsy surgery at our center. In the course of time 32 patients (5,5%) died (10 female (31%)). Median duration of disease at surgery was 36y (0-32y), median age at surgery 40y (18-63y). Temporal lobe resections were performed in the majority of patients (21/65%). At last known timepoint 41% of patients were seizure-free (ILAE outcome class 1a and 1), 50% of patients improved, achieving outcome class 2-4. In 3 patients vagus nerve stimulator (VNS) was implanted after surgical failure. Death in most seizure-free and in half of non-seizure-free patients was not epilepsy-related, although not significantly (p=0.53). Causes of death in 11 patients (34.4%) was directly related to epilepsy (death in seizures, incl. drowning in seizure, status epilepticus, injuries as consequence of seizures etc.). In 4 patients (12%) autopsies were performed and in additional 6 cases (18%) coroner’s inquest reports were available.

Conclusion: Postoperative persistent seizures are associated with higher mortality. Even in seizure-free patients the risk of SUDEP remains. Collaborative effort is needed to promote awareness and education about epilepsy related mortality and to develop, evaluate and implement effective preventive measures.
**Pseudoresistance in idiopathic generalized epilepsies**

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**Purpose:** The aim of the study was to determine risk factors associated with pseudoresistance in a representative cohort of patients with idiopathic generalized epilepsy (IGE) and the impact of pseudoresistance on socioeconomic parameters.

**Methods:** We performed a literature review on definitions of pseudoresistance in IGE. In an established cohort of IGE patients from Funen, current or previous pseudoresistant patients were retrospectively identified based on a comprehensive evaluation of the patients’ medical records and direct patient contact, if required. In addition, clinical characteristics, socioeconomic and demographic data were assessed. Personal interviews were used to determine the brief version of Barratts (BIS-8) impulsivity score.

**Results:** The literature review provided the following definition of pseudoresistance: Seizures due to (I) lacking adherence to anti-seizure medication (ASM), (II) incompliance to general rules of conduct, (III) clinical suspicion of psychogenic non-epileptic seizures, (IV) inadequate choice of ASM/dosage, and (V) incorrect classification of epilepsy. Applying criteria I-III to a cohort of IGE patients (n=499), 73 patients (14.6%) were currently pseudoresistant and 62 (12.4%) were previously pseudoresistant but currently seizure free. Current pseudoresistance was associated with younger age, drug/alcohol abuse, lower rate of full-time employment and higher BIS-8 scores. We found no associations of pseudoresistance with juvenile myoclonic epilepsy, psychiatric disease, specific seizure types or number of seizure types. Previously pseudoresistant patients have tried more ASM and were characterized by male preponderance, higher BIS-8 and higher rates of abuse. Surrogate markers for social outcome did not differ.

**Conclusion:** In IGE, pseudoresistance is associated with young age, drug/alcohol abuse and higher scores for impulsivity. If transient, its impact on socioeconomic status remains limited but may be associated with a risk of overtreatment with ASM.

**Use of machine learning for predicting levetiracetam treatment outcome in temporal lobe epilepsy**

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**Purpose:** To determine the predictive power for seizure-freedom of 19-channels EEG, measured both before and after three months the initiation of the use of Levetiracetam (LEV), in a population of newly diagnosed temporal lobe epilepsy (TLE) people using a machine-learning approach.

**Methods:** Twenty-three individuals with TLE were examined. Clinical outcome was dichotomized into seizure-free (SF) and non-seizure-free (NSF) after two years of LEV. EEG effective power in different frequency bands was compared using baseline EEG (T0) and the EEG after three months of LEV therapy (T1) between SF and NSF patients. Partial Least Square (PLS) analysis was used to test and validate the prediction of the model for clinical outcome.

**Results:** A total of 152 features were extracted from the EEG recordings. When considering only the features calculated at T1, a predictive power for seizure-freedom (AUC = 0.750) was obtained. When employing both T0 and T1 features, an AUC = 0.800 was obtained.

**Conclusions:** This study provides a proof-of-concept pipeline for predicting the clinical response to anti-seizure medications in people with epilepsy. Future studies may benefit from the pipeline proposed in this study in order to develop a model that can match each patient to the most effective anti-seizure treatment.
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Immunotherapy responses of patients with suspected autoimmune-associated epilepsy
with negative neural antibody testing

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Purpose: In patients with refractory epilepsy with negative neural antibody testing, immunotherapy trials may still be pursued in case of a possible autoimmune-associated etiology. The value of immunotherapy trials in such patients remains unclear. For this reason, we reviewed the immunotherapy responses of these seronegative epilepsy patients at our center.

Methods: Retrospective review of epilepsy patients admitted to the Western University Epilepsy Monitoring Unit between 2018 and 2021 who received immunotherapy trials. All had negative or clinically irrelevant results on neural antibody testing and received immunotherapy (methylprednisolone (IVMP) or immune globulin (IVIg) or plasma exchange (PLEX) or rituximab). We considered patients responders when their seizure reduction was ≥ 50%.

Results: Fourteen patients were identified. Of them, 50% (n=7) were female, with a median age of 43.5 years (IQR= 28.75-63.25). All were refractory to ≥ 2 anti-seizure medications. Median age of epilepsy onset was 39.5 years (IQR=23.75-60.25). Median time from epilepsy diagnosis until received immunotherapy was 15.5 months (IQR=12.75 -21.75). Patients received either IVIG and IVMP (35.7%, n=5) or IVIG alone (28.5%, n=4) or IVIG, IVMP and PLEX (21.4%, n=3) or IVMP alone (7.1%, n=1) or IVIG,IVMP and rituximab (7.1%, n=1). Median follow-up duration was 25 months (IQR=24-31.25). Although non-sustained early immunotherapy responses were common, sustained response to immunotherapy at last follow-up was only observed in 21.4% (n=3). Factors confounding determination of immunotherapy efficacy were present in all three of these cases (e.g: concurrent changes in ASM, lack of temporal relationship between immunotherapy administration and seizure reduction).

Conclusion: Our findings suggest that immunotherapy trials in patients with suspected autoimmune-associated epilepsy but with negative neural antibody testing are largely unsuccessful. This data suggests an insufficient therapeutic effect after immunomodulatory treatment or, alternatively, non-immune-mediated mechanisms are causing this type of epilepsy. Critical evaluations of immunotherapy trials in patients with suspected autoimmune-associated epilepsy with negative neural antibody testing are needed.

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Prevalence and risk factors of post stroke epilepsy in young population in Taiwan

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Purpose: The incidence of ischemic stroke has increased in the young population in the recent 20 years. Post-stroke epilepsy (PSE) is a common complication after stroke. However, there is a lack of population-based studies with sufficiently long follow-up on PSE occurrence in young adults. Accordingly, this study aimed to investigate the long-term incidence and risk factors for the occurrence of PSE in these aged group.

Method: The retrospective cohort study was conducted using Taiwan National Health Insurance Research Database (NHIRD) between 2002 and 2018. All patients aged 19-44 who were diagnosed with the International Classification of Disease, 9th revision Clinical Modification (ICD-9-CM) codes of ischemic stroke from 2002 to 2015 were enrolled with at least three years follow-up. Multivariable Cox regression models were performed to identify factors associated with PSE, including patients' demographic data, stroke severity, etiologies/comorbidities, and behavioral risk factors.

Results: 402 young adults (6.2%) with PSE were found in this study. Stroke severity was associated with PSE, including seizure at first stroke admission (adjusted hazard ratio [aHR], 57.58; 95% CI, 43.19–76.75), National Institutes of Health Stroke Scale (NIHSS) score ≥10 (aHR, 1.98; 95% CI, 1.50–2.61), length of stay ≥ 14 days (aHR, 1.60; 95% CI, 1.27–2.03), recurrent stroke (aHR, 2.33; 95% CI, 1.87–2.91), and language disorders (aHR, 1.80; 95% CI, 1.23–2.65). Furthermore, stroke patients with drug abuse were 2.76 times more likely to develop PSE than those without (aHR, 2.76; 95% CI, 1.12–6.80). In contrast, using statin (aHR, 0.56; 95% CI, 0.41–0.74) is associated with a lower risk of PSE.

Conclusion: Stroke severity and drug abuse are associated increased risk of PSE in young population. Reducing the severity of stroke, using statin and controlling behavioral risk factors might be able to decrease the risk of PSE.
**The EPilepsy outcome Set for Effectiveness Trials project (EPSET): developing a core outcome set for adults with epilepsy**

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**Purpose:** A Core Outcome Set (COS) is a standardised list of outcomes that should be reported as a minimum in all trials. In epilepsy, the choice of outcomes varies widely among existing studies, particularly in randomised controlled trials (RCT). This diminishes opportunities for informed decision making, contributes to research waste and is a barrier to integrating findings from multiple RCTs in systematic reviews and meta analyses. COS facilitate the undertaking of trials that are relevant to patients and health services and help standardise trial methodology so more meaningful results can be obtained.

**Method:** Given that no COS for adults with epilepsy exists, we are developing an internationally derived COS specific to treatment trials for adults with epilepsy (www.epsetproject.org). We have undertaken a rapid review of the qualitative literature exploring experiences of people with epilepsy (PWE), to identify core concepts that map to potential measurable outcomes. We have also undertaken rapid review of outcomes already measured in phase 3 and phase 4 epilepsy specific RCTs to generate a long list of potential measurable outcomes to take to an international consensus process. International stakeholder groups involved include health care professionals, PWE, their representatives and researchers. Consensus is being ascertained by a two-round online modified Delphi survey and consensus meeting to ratify a final COS that is representative of all stakeholder views.

**Results:** The results of the COS will be used to inform the recommendation of specific measurement instruments to measure each of the outcomes identified as core.

**Conclusion:** Developing a COS for adults with epilepsy and deriving international consensus will ensure that meaningful outcomes are measured in future RCTs, ensure that the results of trials are relevant to the needs of PWE, reduce research waste and ensure that the results of trials assessing the same treatment can be combined in meaningful ways.

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**Risk assessment of sudden death in epilepsy, a literature overview**

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**Purpose:** The purpose was to explore the tools developed to assess risk of Sudden Death in epilepsy (SUDEP) to help physician make the best use of available tools to inform patient of the risk and adapt care accordingly.

**Method:** A literature overview was performed to identify tools developed to assess risk of SUDEP in patient. Risk scores, Check list of risk factors and risk prediction model published were screened from MEDLINE.

**Results:** The SUDEP-7 inventory was proposed in 2010 but without validation and with poor predicting abilities. Recently the SUDEP-3 inventory presented with better discrimination capabilities, measured by the area under the receiving operator curve (AUROC), than SUDEP-7 inventory (SUDEP-7: 0.66 (0.54-0.87); SUDEP-3: 0.75 (0.64-0.86). Three well known risk factors were included: GTC seizure frequency, seizure of any type during the past year and intellectual disability. Jha et al. also proposed a model for the prediction of SUDEP including 22 predictors with an AUROC of 0.71 (.68-.74), but its clinical use seems unpractical. Another interesting tool has been developed in the UK by Shankar et al.: the safety checklist. Designed to optimise the care of patients with epilepsy. It lists potential or known risk factors in order to engage in discussion with the patient to mitigate risk when possible.

**Conclusion:** Several tools have been developed in the past few years, and while heterogeneous they can help guide physician to improve information and care given to patient. Improvement of existing tools are to be expected, targeted at more specific population or including new identified risk factors like nocturnal seizures.
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Quantitative EEG analysis in the differential diagnosis of acute amnestic syndromes

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Purpose: Acute amnestic syndromes are transient and mostly reversible disorders of short-term episodic memory caused by different etiologies, such as a hypoxic insult of vascular nature (the so-called transient global amnesia or TGA) or a focal critical activity (the so-called transient epileptic amnesia or TEA). Due to the low sensitivity of standard EEG recording in inter-ictal anomalies identification after an ictal amnesic disorder, the differential diagnosis between these two distinct clinical entities can be challenging. The present study aims to determine whether quantitative EEG analysis could aid clinicians in the differential diagnosis of acute amnestic syndromes.

Method: We collected 19 channel EEGs recordings from 19 patients with TEA and 21 patients affected by TGA. We computed Power Spectrum Density (PSD) measures for all 19 channels (Global PSD) and specifically for temporal electrodes T3 and T4 (Regional PSD). We also compared PSD of patients with TEA and TGA for each frequency band, both for global and regional spectrum. Finally, ROC curves models were built to test whether quantitative EEG parameters could aid in the distinction between TEA and TGA.

Results: Quantitative EEG analysis revealed a significant increase of PSD in Theta power in patients with TGA when compared with TEA, both in Global and Regional PSD (p<0.05). ROC curve analysis of theta relative power revealed an AUC of 0.7494 (95% CI: 0.5865-0.8872) and 0.7018 (95% CI: 0.5263-0.8596) for Global PSD and Regional PSD, respectively.

Conclusion: Receiver operating characteristic (ROC) curves of theta spectral power demonstrated that the EEG power spectrum can provide a useful tool to differentiate patients with TEA from those with TGA. If implemented, quantitative EEG analysis could become a promising tool to help clinicians in the differential diagnosis of acute amnestic syndromes in the emergency setting.

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Neuropsychological and Electroencephalographic effects of adjunctive Cenobamate treatment: data from an ongoing prospective observational study

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Purpose: Drug resistant epilepsy (DRE) is a condition interesting almost a third of people with epilepsy (PwE) with important implications in terms of morbidity and mortality. Cenobamate (CB) is a novel oral antiseizure medication (ASM) approved in Europe as adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult people with DRE. The goal of this ongoing prospective observational study is to evaluate clinical and neurophysiological response in people who introduce CB through medical examination, neuropsychological assessment, and quantitative EEG (qEEG) analysis.

Method: We enroll adult people with DRE with focal onset seizures. Before introduction of CB (T0) and after three (T1) and six months (T2), in the context of a medical examination, we record seizures frequency, the presence of adverse events (AEs) and therapeutic changes. At the same time the following clinical scales are administered: EpiTrack, Quality of life in epilepsy (QOLIE-31), Beck Depression Inventory – II (BDI-II), Generalized Anxiety Disorder 7-item (GAD-7), Pittsburgh Sleep Quality Index (PSQI) and 14-item Resilience Scale (RS-14). A nineteen channel-EEG recording is acquired at T0, T1 and T2 to perform a further qEEG analysis of power spectral density (PSD) and global EEG connectivity.

Results: On the 20th of January 2022 we have enrolled ten people with DRE with focal onset seizures, three women and seven men, with age ranging from 25 to 58 years (median age of 50.5), in therapy with at least 2 ASMs (mean of 3 ASMs). Nine of them are also in therapy with vagal nerve stimulation (VNS). To date only one of them has reached the three months follow-up.

Conclusion: We will discuss the results of this study by highlighting the impact of adjunctive CB treatment on cognitive functions, emotional aspects, and any possible modifications in term of EEG activity and connectivity related to the introduction of CB.
Risk factors for epilepsy after aneurismal subarachnoid hemorrhage

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Purpose: Subarachnoid hemorrhage (SAH) is a severe illness that comprises only 3-5% of all strokes but leads to >27% of stroke-related life years lost before age 65. In this context, epileptic seizures have been associated with a negative effect over functional and vital prognosis, as well as cognitive decline. Early identification of those patients prone to seizures might enable us to develop preventive or second prophylaxis strategies. Our aim is to describe the factors associated with greater risk of epilepsy development after the occurrence of an acute aneurysmal SAH (aSAH).

Methods: This is a retrospective, observational study of adult patients with aSAH admitted to our center between February 2017 and December 2020. We collected demographics, clinical onset features, common scores (Fisher, WFNS…), radiological variables, acute symptomatic (<7 days after onset) and remote (>7 days) unprovoked seizures (i.e., epilepsy). Using multiple Cox regression analysis, we identified factors independently associated with epilepsy development.

Results: We included 179 patients with aSAH (mean age 60 (+/-14), 64% female). Twenty-four percent presented acute symptomatic seizures and 29% died during admission. Patients with previous epilepsy (3) and/or loss to follow-up due to death (52) or transfer (3) were excluded for the subsequent analysis of epilepsy. Of the remaining 121 subjects (median follow-up 1062 days), fifteen patients developed epilepsy (12.4%) with a median latency of 249 days (106-444). Independent risk factors were acute symptomatic seizures (HR 4.2[1.4-12.8], p=0.012), middle cerebral artery aneurisms (HR 5.8[1.8-18.5], p=0.003), a “red” Vasograde score (HR 9.5[2.8-32.9], p<0.001) and history of epilepsy predisposing factors (e.g., febrile seizures, head trauma) (HR 11.8[2.8-50.2], p=0.001).

Conclusion: Both patient and SAH-related factors seem to be involved in greater risk of epilepsy. Prognostic multivariable scores including those features may provide additional information for future preventive treatment guidelines and may increase knowledge about epileptogenesis in SAH-related epilepsy.

Drug-resistant temporal lobe epilepsy: analysis of morphological results in operated adult patients

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Purpose: The purpose of this study is to clarify the morphological features of tissues removed during surgery in patients with drug-resistant temporal lobe epilepsy.

Methods: We studied biopsy specimens from 73 operated patients with focal temporal lobe drug-resistant epilepsy. In all cases, standard histological studies of tissue removed during surgery and Immunohistochemistry (IHC) were performed. In some cases, electron microscopy was also used.

Results: A total of 73 patients aged 19 to 52 years with structural drug-resistant temporal lobe epilepsy were examined and operated on. Focal cortical dysplasia (FCD) detected in 18 patients. In 6 cases, mesial temporal sclerosis (MTS) occurred. Changes in neuroglia in epileptic foci deserve special attention. Using Immunohistochemistry (IHC) and electron microscopy, we detected a large number of neurons in the cerebral cortex with signs of apoptosis at different stages of this process. Apoptotic changes in glial cells were observed predominantly in oligodendrocytes in both the cortex and the white matter of the brain. During the study of astrocytic glia changes we made clinical and morphological correlations. We found that patients with a severe course of the disease (and sometimes with a history of status epilepticus) had a very mild astrocytic reaction with foci of demyelination in the cortex and subcortical. In contrast, in patients with a milder course of epilepsy without a history of status epilepticus, astrocytic-glial reactions were very pronounced.

Conclusion: According to our studies, astrocytic gliosis in epileptic foci in structural drug-resistant focal temporal lobe epilepsy is not pathological, but an adaptive (protective) reaction. In general, changes in the neuroglia in the epileptic focus in drug-resistant epilepsy have significant manifestations, which has an impact on the progression of the disease.

Disclosure. The project was performed under the state task #121031000359-3 of Almazov National Medical Research Centre, Saint Petersburg, Russian Federation.
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Seizure prediction after a first unprovoked epileptic seizure: current status of the Swiss First Study

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If patients present with a first unprovoked epileptic seizure, uncertainty is a frequent companion for the patient and the caregiver. Diagnosing an epileptic seizure is challenging, since epileptiform discharges, the best objective biomarker are rarely detectable. Estimating seizure recurrence, and therefore diagnosing epilepsy, is even more sophisticated. The risk for seizure recurrence can be estimated, but not precisely calculated with the present diagnostics. Therefore, after a first seizure it often cannot be distinguished if anti-seizure medication is inevitable or not necessary.

In the ongoing Swiss First study, we prospectively analyze patients with a suspected first unprovoked epileptic seizure, review their MRI and EEG data, and observe them over a period of two years. We screen for potentially epileptogenic lesions within the MRIs. We additionally apply automatic brain morphometry and a novel MRI-sequence to detect electric high-frequency oscillations. EEGs are analyzed regarding functional connectivity and microstate-architecture. After the observational period, multimodal data from the work packages are employed to set up a deep-learning algorithm to predict the individual risk of seizure recurrence based on clinical and quantitative features.

The aim of this study is to prospectively investigate clinical, EEG- and neuroimaging based feature sets associated with an epileptic seizure and to identify patients at risk for manifestation of epilepsy. Currently, approx. 400 patients have been included in the Swiss First study, and the study is open until the end of December 2022. Diagnosis posed at the emergency department was upheld in only 73%, showing us the large potential in diagnostics. Also, 41 patients had subsequent seizures, that could have potentially prevented by establishing antiseizure medication. We will present the preliminary outcomes of these patients and show, in what setting our diagnostic tools can be applied in clinical environment.

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Increased prevalence of minor physical anomalies in patients with epilepsy - results with the Méhes Scale

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Purpose: The aim was to investigate the rate and topological profile of minor physical anomalies (MPAs) in adult patients with epilepsy with the use of the Méhes Scale, a comprehensive modern scale of dysmorphology.

Methods: Consecutive epilepsy patients admitted for outpatient evaluation were included. Patients with comorbidities of neurodevelopmental origin (such as autism, severe intellectual disability, attention deficit hyperactivity disorder, schizophrenia, tic disorder, Tourette syndrome, bipolar disorder, specific learning disorder and specific language impairment) were excluded. All participants underwent physical examination with the use of the Méhes Scale for evaluation of MPAs, including 57 minor signs. The frequency and topological profile of MPAs were correlated to clinical patient data.

Results: 235 patients were included, according to the following subgroups: acquired epilepsy (non-genetic, non-developmental etiology) [N=63], temporal lobe epilepsy with hippocampal sclerosis (TLE with HS) [N=27], epilepsy with cortical dysgenesis etiology [N=29], cryptogenic epilepsy [N=69] and idiopathic generalized epilepsy (IGE) [N=47]. As controls, 30 healthy adults were recruited. The frequency of MPAs were significantly affected by the type of epilepsy [H(6)=90.17; p<0.001]. Pairwise comparisons showed that all patient groups except for acquired epilepsy were more common associated with increased frequency of MPAs (p<0.001 in all cases). Furrowed tongue and high arched palate were more common compared to controls in all epilepsy subgroup except for TLE (p<0.001 or p=0.001 in all cases). A positive association was detected between the occurrence of MPAs and antiepileptic drug therapy resistance [Exp(B)=1.19; CI 95% 1.37 – 12.80; p=0.012].

Conclusion: MPAs are more common in patients with epilepsy, which corroborates the emerging concept of epilepsy as a neurodevelopmental disorder. Assessment of these signs may contribute to the clarification of the underlying etiology. Moreover, as increased frequency of MPAs may indicate pharmacoresistance, the identification of patients with high number of MPAs could allow evaluation for non-pharmacological treatment in time.
Outcome in bilateral temporal lobe epilepsy after treatment with vagus nerve stimulation

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Introduction and purpose: The most common type of therapy-resistant epilepsy is temporal lobe epilepsy (TLE). Unilateral TLE usually has a favourable prognosis with resective surgery. However, surgery is usually not considered in cases of bilateral temporal lobe epilepsy (bi-TLE) which occurs in 10–20% of patients with TLE. Vagus nerve stimulation (VNS) is approved as a palliative therapeutic option. The outcome of treating bi-TLE with VNS is unknown. Our study evaluates the effect of VNS on the reduction of seizure frequency in therapy-resistant epilepsy patients with bi-TLE.

Method: This retrospective study included all patients with bi-TLE who underwent VNS implantation at Western University Hospital from 1997 to 2019. The main outcome was reduction in seizure frequency.

Result: Our study included 17 patients (11 women). The mean seizure onset age was 19.4 years (SD=12.99). Bi-TLE was confirmed by scalp EEG in 8 cases (47%) and invasive recording in 9 (52.9%). The mean follow-up was 48.11 months (SD=59.49). The mean seizure frequency per month before VNS was 8.75/m, and after VNS stimulation was 2.64/m. Compared to the baseline, 11 individuals (64.7%) achieved at least 60% reduction in seizure frequency. None of our patients became seizure-free. Six patients (35.3%) experienced either no or minimal reduction in seizure frequency. The responder rate was 87.5% in those who underwent scalp EEG only and 55.5% in those who underwent invasive EEG. Side effects were reported in 10 patients (58.8%). Side effects included mild coughing and hoarseness. In one case, post-surgical wound infection was documented and managed with a brief course of antibiotics.

Conclusions: In therapy-resistant BI-TLE therapeutic choices are restricted. VNS was shown to be safe and beneficial as an additional treatment in this group of patients.

Can disruption of basal ganglia-thalamocortical circuit in Wilson disease be associated with Juvenile myoclonic epilepsy phenotype?

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Purpose: Here we describe multimodal MRI analysis in a patient with Wilson disease and a seizure disorder characterized by an electroclinical picture resembling Juvenile Myoclonic Epilepsy, whose brain structural MRI showed deposition of ferromagnetic materials in the basal ganglia, with marked hypointensities in T2-weighted images of globus pallidus internus bilaterally.

Method: A multimodal MRI study using voxel-based morphometry (VBM) and fMRI resting state analysis was performed, to investigate structural and functional cortico-subcortical connectivity of the patient. A group of 30 healthy women (mean age 35.4± 10 years) with no history of neurological or psychiatric diseases were recruited as controls.

Results: Resting-state fMRI study revealed increased functional connectivity in patient with respect to healthy controls: 1) between the primary motor cortex and several cortical regions, including the secondary somatosensory cortex, 2) between the globus pallidus and the thalamo-frontal network. These functional changes were not paralleled by modifications of cortical and subcortical volumes in the VBM analysis.

Conclusion: Our findings suggest that globus pallidus alterations due to metal accumulation can lead to a reduction of the normal globus pallidus inhibitory tone on the thalamo-(motor)-cortical pathway. This in turn can result in hyperconnectivity in the motor cortex circuitry, leading to myoclonus and tonic-clonic seizures. We suppose that, in this patient, Wilson disease generated a ‘lesion model’ of myoclonic epilepsy.
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Long-term safety and tolerability of eslicarbazepine acetate in an Asian adult population with focal seizures: results from a randomized, double-blind, placebo-controlled study with two open label parts

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Purpose: Evaluate the long-term safety/tolerability of adjunctive eslicarbazepine acetate (ESL) treatment in Asian adult patients with refractory focal seizures.

Methods: Study BIA-2093-304 was a randomized, double-blind (DB), placebo-controlled trial of 14 weeks (Part I) with two subsequent long-term open-label (OLE) periods: Part II (1 year); Part III (at least 2 years). Safety/tolerability were assessed during the DB and OLE periods and included the evaluation of treatment-emergent adverse events (TEAEs).

Results: Part I safety population was composed by 650 patients; 125 (19.2%) were Asian (45 placebo; 41 ESL 800mg; 39 ESL 1200mg). Safety population of Parts II and III contained respectively 92 (73.6%) and 23 (18.4%) Asian patients.

TEAEs were reported by 64% (n=80), 71.7% (n=66) and 87% (n=20) of the Asian patients during Part I, Part II and Part III; while related TEAEs were reported by 46.4% (n=58), 45.7% (n=42) and 17.4% (n=4) of these patients in each part, respectively. Most frequent related TEAEs were: dizziness (4.4% placebo vs. 22.5% ESL arms), somnolence (2.2% placebo vs. 15% ESL arms) and headache (2.2% placebo vs. 7.5% ESL arms) in Part I, dizziness (18.5%), somnolence (12%) and headache (2.4%) in Part II, and diplopia (4.3%), dizziness (4.3%) and insomnia (4.3%) in Part III. Serious related TEAEs were: leukocytoclastic vasculitis (n=1) in Part I, somnolence (n=1) in Part II and one patient presented two serious TEAEs (dizziness and vomiting) in Part III. These serious TEAEs led to discontinuation of the patients in Part I and II, but not in Part III.

Additionally, most TEAEs were of mild or moderate intensity. No TEAEs led to death of patients.

Conclusion: Long-term safety/tolerability with adjunctive ESL treatment in an Asian adult population with refractory focal seizures was consistent with the known safety profile of ESL for other ethnicities, with no new or unexpected safety finding emerging in this setting.

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A mobile and wearable app to forecast seizure risk: a real-world validation and usability study

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Purpose: The unpredictability of seizures is debilitating for people with epilepsy. Accurate seizure forecasters could improve quality of life, but must be practical for long-term. We developed a wearable and mobile app to forecast seizure risk using cycles of seizure likelihood.

Method: The forecasting pipeline was deployed on a cloud platform capable of updating seizure risk in a scalable, real-world mobile application. To validate feasibility, forecasts were run ‘under-the-hood’ for a cohort of users (without displaying seizure risk)

A subset of users with sufficient data were selected to validate performance of two implementations of risk forecasts: a diary-based forecast, using self-reported seizure times, and a diary+wearable forecast which included signals from a smartwatch. The diary-based forecaster used self-reported seizure times to detect multiday cycles. The diary+wearable forecaster augmented these seizure cycles with cycles of heart rate. Individuals’ seizure cycles were converted to a continuous likelihood score likelihood (between 0 and 1) and seizure risk (low, medium, high).

Forecasts were initially trained on 10 seizures, then iteratively tested and updated with subsequent reported events.

Results: Seizure risk forecasts were run continuously for 460 app users over a 6-month period. Forecasts were updated weekly and after each seizure, taking between 1-10s per user.

The diary-based forecaster was assessed for 45 participants (mean test seizures: 128.2). Mean AUC was 0.675 [IQR: 0.64-0.721] with an average sensitivity of 47.5% and average specificity of 76.4%.

The diary+wearable risk forecaster was assessed for 13 participants (mean test seizures: 94.6). Mean AUC was 0.714 [IQR: 0.62-0.83] with an average sensitivity of 56.0% and average specificity of 77%.

Conclusion: This study represents the first prospective deployment of non-invasive seizure forecasts in a mobile application. The app is scalable for clinical use, with reasonable forecast accuracy. Future work will initiate a prospective clinical trial for a seizure risk app.
Vagus nerve stimulation (VNS) in genetic epilepsies: approach in highly specialized centers around the world

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Purpose: Seizures represent a core symptom of genetic epilepsies that can impact cognitive function. This impact is exacerbated by interictal epileptiform activity and the neurobiological process behind the epilepsy. This is referred to as developmental and epileptic encephalopathy (DEE), which is often related to gene variants and mostly childhood-onset.

Vagus Nerve Stimulation (VNS) has shown positive effects for the treatment of some well-known genetic DEE such as Dravet Syndrome and Lennox Gastaut Syndrome.

Aim of this analysis is to describe for the first-time patients with genetic epilepsies treated with VNS Therapy to offer greater insight into the status quo of genetic testing in drug-resistant epilepsy and into the genetic basis of patients treated with VNS Therapy around the world.

Methods: We collected and analyzed clinical data of patients with genetic or suspected genetic epilepsies enrolled in the Comprehensive Outcomes Registry in Subjects with Epilepsy Treated with Vagus Nerve Stimulation Therapy (CORE-VNS, NCT 03529045). CORE-VNS is a prospective registry collecting data from patients with drug-resistant epilepsies treated with VNS.

Results: A total of 828 patients consented to participate in this study between May-2018 and June-2021 in 61 centers in 15 countries. 253 (30.6%) patients underwent genetic testing and within this group, 115 (45.5%) were carrying a genetic variant likely correlated with the epilepsy phenotype (genetic epilepsy group). 14 (5.5%) carried a genetic variant of uncertain significance. Mutations of SCN1A and TSC2 genes were the most frequent (n=15). In the genetic epilepsy group, epilepsy diagnosis was made before age 4 in 73.9% of patients and the most frequently reported epilepsy syndromes were Tuberous Sclerosis (14.8%), Dravet Syndrome (10.4%), Lennox Gastaut Syndrome (9.6%) and Infantile Spasms/West Syndrome (7.0%).

Conclusions: This analysis shows that VNS Therapy is used to treat patients with genetic epilepsies worldwide and considered in the early phase of disease evolution.

Interictal autonomic dysfunction is not associated with the frequency of focal-to-bilateral tonic-clonic seizures

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Purpose: Interictal autonomic dysfunction might contribute to sudden unexpected death in epilepsy patients. The risk of sudden death is increasing with the frequency of bilateral tonic-clonic seizures (BTCS) (Harden et al. Neurology 2017;88(17):1674-1680). We aimed to evaluate the correlation between autonomic cardiovascular regulation and frequency of BTCS in patients with focal epilepsy.

Method: In 40 patients with BTCS and documented focal epileptiform electroencephalographic activity (mean age 34.7±9.0 years, 16 males, median frequency of BTCS 4 seizures/year with interquartile range 1–12 seizures/year) and 33 healthy controls (mean age 31.8±7.0 years, 13 males), we recorded RR-intervals (RRI), beat-to-beat systolic blood pressure (BPsys), and respiratory frequency during 5 minutes at supine rest, during 75 seconds of metronomic breathing, and upon active standing. We calculated RRI-standard-deviation (RRI-SD), RRI-coefficient-of-variation (RRI-CV), total-RRI-powers (RRI-TP) reflecting total cardiac autonomic modulation, low-frequency-powers of RRI-modulation (RRI-LF) and of BPsys-modulation (BPsys-LF) reflecting sympathetic modulation, root-mean-square-of-successive-RRI-differences (RMSSD), high-frequency-powers of RRI-modulation (RRI-HF) and RRI-expiration:inspiration-ratio (E:I-ratio) reflecting parasympathetic modulation, supine and standing baroreflex sensitivity (BRS), and RRI-30:15-ratio reflecting baroreflex response to active standing. We compared autonomic parameters between patients and controls (Mann-Whitney-U-test; significance: p<0.05) and assessed correlation between autonomic parameters and frequency of BTCS (Spearman rank correlation; significance: p<0.05).

Results: Compared to controls, patients had all the above parameters significantly decreased. The most prominent decrease with p<0.001 was observed in RRI-SD, RRI-CV, RMSSD, RRI-HF, RRI-LF, RRI-TP. Frequency of BTCS did not correlate with any autonomic parameter.
Conclusion: Patients with focal epilepsy had impaired interictal autonomic cardiovascular regulation. However, the frequency of focal-to-bilateral tonic-clonic seizures did not correlate with the severity of interictal autonomic dysfunction. Acknowledgement: We are grateful to Professor Max Hilz (Erlangen, Germany) for the invaluable support regarding this work.

Are ultra long-term EEG devices suitable for the job to be done?

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Purpose: To investigate whether the current version of the novel subcutaneous ultra long-term EEG device is useful for epileptologists and what needs to be improved.

Method: Five epileptologists met at a roundtable meeting to assess the novel subcutaneous ultra long-term EEG devices and to discuss what patients they are suitable for. Findings from the meeting were recently published (Pathmanathan et al., Front Neurol, 2022, Epub). After the meeting each epileptologist answered a questionnaire on their personal preferences regarding whether they would use it in clinical practice and what needed to be improved.

Results: All participants found the device useful in their clinic. The primary use-case would be to assess response to treatment by more accurately than a diary provide a number for seizures occurred. This would especially be relevant in cases where the patient is drug resistant and there is a suspicion of unrealized seizures. On top of that, objective understanding of circadian and multiday periodicities can be used to guide epilepsy management. For the next generation of devices, there was a wish among all participants for bilateral recordings which would convert the technology from a monitoring tool to a localization and diagnostic tool. Furthermore, the participants thought sleep, interictal epileptiform discharge, and heart rate change analysis would add to the value offer of the subcutaneous ultra long-term EEG devices.

Conclusion: The job to be done for the subcutaneous ultra long-term EEG device available on the European market today is to objectively and more accurately than seizure diaries to assess how many seizures a person with epilepsy has. This is answered adequately with the current version of the device.
Comparing communication in face-to-face and telephone epilepsy consultations

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Purpose: Covid-19 has enforced a widespread shift from face-to-face to telephone epilepsy consultations. Earlier research has explored patients’ and clinicians’ views of teleneurology, but there has been no research directly examining the impact of remote consultations on neurologist patient communication. The purpose of this research is to understand the similarities and differences between these two types of epilepsy consultation by comparing recordings and transcripts of conversations.

Methods: Conversation analysis of recorded telephone (n=36) and face-to-face (n=61) epilepsy consultations. Telephone consultations captured in Sheffield, UK, in 2021 featuring 6 clinicians were compared with face-to-face recordings recorded in Sheffield and Glasgow in 2012.

Results: There were no significant differences in either the duration or total number of words spoken in face-to-face and telephone consultations. Patients did, however, ask significantly fewer questions in telephone consultations (p < 0.001) and questions asked over the telephone were qualitatively more likely to be about practical matters and less likely to prompt topic shifts in the conversation, suggesting lower levels of patient engagement and participation. In addition, there was qualitative evidence that telephone consultations involving companions were more difficult to conduct than face-to-face interactions including third parties.

Conclusion: Although face-to-face and telephone epilepsy consultations are similar in their overall structure, the telephone does seem to impede certain aspects of neurologist-patient interaction. Neurologists can take steps to address this by directly eliciting patients’ questions and facilitating companion participation.

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Asymmetric sleep in patients with focal epilepsy

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Purpose: Sleep is a focal phenomenon and sleep biomarkers engage delimited brain regions. While this has been extensively studied in physiological paradigms, the local disruption of sleep by pathological processes is yet to be fully unveiled. Here, we investigated whether epilepsy, which is itself modulated by sleep, can in turn be associated with a perturbed expression of sleep biomarkers.

Method: From our presurgical evaluation EEG database, we retrospectively included seventy-four patients (32 females) with a lateralized epileptic focus (36 left-sided). We compared, between patients with left vs right focal epilepsy, the inter-hemispheric asymmetry of sleep slow oscillations power (0.5-4 Hz); spindles density (occurrence per min), amplitude, duration and locking to slow oscillations (estimated through the intertrial coherence); and sleep slow waves density, amplitude, duration and slope. We used a Fine Tree classifier to test if the asymmetry of the sleep biomarkers features can predict left vs right focal epilepsy.

Results: Only right focal epilepsy showed an asymmetry of slow oscillations power in favour of the epileptic hemisphere (p=0.0152). Furthermore, we identified significant inter-hemispheric asymmetries for spindle density (higher in the non-epileptic hemisphere, p<0.0001), amplitude (higher in the epileptic hemisphere, p=0.0128) and duration (longer in the non-epileptic hemisphere, p=0.0151) as well as for slow wave amplitude (higher in the epileptic hemisphere, p=0.0142) and slope (steeper in the epileptic hemisphere, p=0.0099). The classifier was able to cluster left vs right focal epilepsy with a 76% accuracy, which was significantly above chance level (p<0.0001, Fisher’s exact test). We provide a composite index, the Epileptic Lateralization Index (ELI), that predicts the lateralization of epilepsy.

Conclusion: We provide a comprehensive profiling of the main sleep electrophysiological biomarkers. Our results suggest that patients with focal epilepsy show significant differences in the expression of the main sleep biomarkers, which can be used to predict epileptic lateralization.
Purpose: Psychogenic nonepileptic seizures (PNES) resemble epileptic seizures but are not due to an underlying epileptic activity; they often coexist alongside epilepsy. We described and summarized the clinical characteristics of patients with PNES as reported in the literature from the outbreak of the COVID-19 pandemic. We evaluated differences between patients with a diagnosis made immediately prior the pandemic (pPNES) and those who were newly diagnosed during it (nPNES).

Methods: Systematic search with individual patient analysis of PNES cases published since the outbreak of the COVID-19 pandemic. MEDLINE (accessed through PubMed), EMBASE, and Google Scholar were searched from December 2019 to November 2021. Differences between pPNES and nPNES were analyzed using Chi-square or Fisher exact test.

Results: Eleven articles were included, with a total of 133 patients (30 males), 106 pPNES (79.7%) and 27 (20.3%) nPNES. In the pPNES group, PNES frequency increased during the COVID-19 pandemic in 20/106 (15%) patients, whereas in 78/106 (58.7%) the frequency remained stable or decreased. No similar data was available for the nPNES group. Compared to the pPNES group, nPNES was associated with a higher risk of SARS-CoV-2 infection (1/106 versus 3/27; p<0.0001) and epilepsy diagnosis (33/106 versus 16/27; p<0.0001), whereas psychiatric comorbidities were less frequent (76/106 versus 1/27; p<0.0001).

Conclusions: During the pandemic, most patients with pPNES remained stable or improved, whereas nPNES were associated with a lower risk of psychiatric comorbidities. These findings might suggest that the COVID-19 pandemic does not negatively affect PNES, possibly due to lower social exposure, with reduced stress. Although probably and inevitably affected by reporting bias, these intriguing findings suggest that, at least in some patients, the COVID-19 pandemic may not necessarily lead to a worsening in the frequency of PNES and quality of life. These results could justify performing observational studies to further elucidate this issue.
The design of a multicentre, double-blind, randomized, placebo-controlled, Phase II trial in the prevention of epilepsy in stroke patients at high risk of unprovoked seizures: anti-epileptogenic effects of eslicarbazepine acetate

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Purpose: Epilepsy is a prevalent neurological disorder with significant morbidity and mortality, but available drug therapies target its symptoms rather than the underlying cause.1 There is yet no approved therapy for individuals at risk of epileptogenesis,2 however in experimental animal models, ESL demonstrated a possible antiepileptogenic effect.3, 4 Stroke is the most common cause of epilepsy in the elderly,5 and 5-15% of all stroke patients experience a seizure within 2 years of the event.6 This phase-II, multicentre, randomized, double-blind, placebo-controlled study aims to assess if the treatment with ESL for 1 month, started within 120 hours after stroke occurrence, changes the incidence of unprovoked seizures (USs) within the first 18 months after randomisation.

Methods: Patients ≥18 years at high risk of developing USs, after acute stroke (intracerebral haemorrhage or ischaemic), will be randomized (1:1) to ESL 800 mg or placebo. Treatment will start within 120 hours after primary stroke occurrence and continue until 1 month after randomization and then is tapered off. Patients will be followed up until 18 months. Exclusion criteria include, amongst others, history of previous clinical cerebral cortical stroke, history of USs prior to stroke or impaired pre-stroke level of function. Primary and key secondary efficacy endpoints include proportion of patients who experience the first US within 6, 12 and 18 months after randomization (failure rate). Sample size is planned to have at least 80% power to demonstrate a significantly lower failure rate under ESL vs. placebo.

Results: Study is planned to include approximately 200 subjects. Clinical phase is ongoing, and recruitment is open in Austria, Germany, Italy, Israel, Portugal, Spain, Sweden and UK.

Conclusion: Following promising experimental results and the need of further research in patients, the antiepileptogenic effect of prophylactic ESL will be investigated in stroke patients at high risk for USs.

Drug concentrations in adult patients with drug-resistant epilepsy treated with old and new generation drugs: association with patient characteristics

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Introduction: We present a group of 49 patients diagnosed with drug-resistant epilepsy, who were either referred to hospital treatment from other neurological clinics or from the outpatient clinic of the Department of Neurology in the Stroke ward and the Neurological Rehabilitation ward of the John Paul II Cracow Specialist Hospital in Cracow, due to poor control of epileptic seizures. In most patients in the past, in the course of the disease pharmacological treatment was repeatedly modified. The main criterion for qualifying patients, was the inadequate control of epileptic seizures despite the use of stable doses, subjected to analysis, anti-epileptic drugs. Patients received: sodium salt of the valproic acid or valproic acid (VPA), lamotrigine (LTG) or levetiracetam (LEV), in addition to other drugs (antiepileptic and non-antiepileptic). In the study group, the concentration of the above mentioned anti-convulsant drugs in the serum and in the cerebrospinal fluid were determined.

Purpose of the study: The aim of a non-randomized clinical pharmacokinetic study was to optimise the dosage of three anti-epileptic drugs in patients with drug-resistant epilepsy based on their serum and cerebrospinal fluid concentrations.

Material and methods: The study group consisted of patients over 18 years of age, of both sexes, diagnosed with drug-resistant epilepsy, in whom the concentration of AED in the blood and cerebrospinal fluid was determined. Patients had been on a stable oral dose of the drug (sodium salt of valproic acid or valproic acid, lamotrigine and levetiracetam) for at least one month, before it was determined.

Conclusions: The determined AED concentrations in 49 patients allowed to estimate the concentrations of the tested drugs in serum and cerebrospinal fluid. On the basis of obtained concentrations and pharmacokinetic parameters in serum, pharmacotherapy was modified which in some patients resulted in an improvement of their clinical condition.
Factors influencing the concentration of valproic acid in patients with diagnosed epilepsy

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Introduction: Factors influencing the concentration of valproic acid in patients with diagnosed epilepsy in the Polish population. Antiepileptic drugs (AEDs) have complex pharmacokinetics and narrow therapeutic ranges, resulting in significant differences in concentrations after administration of therapeutic doses. Valproic acid (VPA) is a widely used AED with non-linear pharmacokinetics requiring therapeutic concentration monitoring (TDM) due to its complex and wide inter-individual pharmacokinetic variability.

Purpose: The aim of the study was to assess the age-related lifestyle on the concentration of VPA in the serum of patients diagnosed with epilepsy.

Methods: The analysis of VPA concentrations was carried out in a group of 33 patients, aged 20 to 71 years, diagnosed with epilepsy. The patients were divided into two groups according to their age. Group I comprised 25 patients aged 20 to 40 years, while group II comprised the remaining 8 patients aged 41-71 years. There was no consistency in the division of age into elderly, young or middle-aged patients. The lack of such a division was the consequence of the small size of the group of elderly patients. According to the adopted old age threshold of 60-65 years, they constituted only 9% of the studied population (3 respondents).

All epilepsy patients were administered VPA in combination (n = 29) with at least one (potentially interacting) other drug, both anti-epileptic and non-anti-epileptic, in 9 patients VPA was the only anti-seizure medication. The plasma concentrations of VPA in all two groups of patients were determined at steady state 0.5 h before the next dose (Cmin) by spectrophotometric method in the commercially available CEDIA® Valproic Acid II Assay (Thermo Scientific).

Results: Lifestyle and age influence the level of serum VPA concentration in patients diagnosed with epilepsy. Rational, personalized antiepileptic drug therapy should consider TDM in all age groups of patients with known epilepsy.

The first documented in Poland mutation of the PDCD10 gene as the cause of multiple cavernous hemangiomas in the brain in a 23-year-old patient

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Introduction: Cerebral vessel malformations constitute a heterogeneous group of inherited pathologies within the central nervous system vessels in terms of structure and function, of which about 15% are cavernous angiomas (Latin cavernous malformation, cavernoma).

We present the case of a 23-year-old patient with mild mental retardation (62-IQ Wechsler), who since reaching the age of majority has been under the care of an adult neurological clinic for periodic control of multiple vascular malformations of the type of cavernous hemangiomas in the brain. In the MRI of the brain in the white matter and subcortex in the frontal and parietal lobes, the patient had multiple vascular malformations of the cavernous hemangioma type.

These pathologies were first described in a 17-year-old patient, and in the previous (before the age of majority) several imaging studies of the brain based on radiographs were suspected in a history of parasitic disease or the presence of calcium salt deposits in the CNS. In the neurological examination, apart from discrete psychomotor retardation, no other abnormalities were found.

Purpose: Determining the basis of multiple vascular malformations of the CNS.

Methods: Sequencing of genome fragments encoding all protein products, as well as the analysis of Single Nucleotide Polymorphisms (SNP) and short insertions and deletions - INDEL (INsertions and DELetions) in the genes from the panel dedicated to the patient showed the presence of the variant meeting the criteria as pathogenic (according to the ACMG recommendation, this is a variant directly related to the development of the disease) - PDCD10 gene.

Conclusions: The mutation of the PDCD 10 gene as the cause of multiple cavernous hemangiomas within the brain is the first documented mutation in this area in Poland. In our country, no mutations confirmed by genetic testing within 3 genes significant for this pathology have been published so far.
Extremely different clinical response in patients with grey matter heterotopia and epilepsy

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Introduction: Grey matter heterotopia is a common type of birth defect, the clinical manifestation of which may be epileptic seizures. In our base we have several dozen patients with epilepsy and grey matter heterotopia. We present the case of two sisters diagnosed with it, who had extreme different clinical responses to antiepileptic treatment.

Purpose: Indication of the cause of various clinical manifestations of epilepsy in sisters with grey matter heterotopia.

Material: An older patient, 35 years old, had poor seizure control. Typical and atypical focal seizures with loss of consciousness occurred at least a dozen times a month, generalized bilateral tonic-clonic seizures with a frequency of up to several per month, with the longest remission lasting several months.

The younger sister, 31, has been seizure free for several years. A genetic test was performed in an elderly patient at the University Hospital in Nice, the presence of a mutation in the FLNA gene coding for filamine A has been confirmed: Heterozygosity of exon 48 of the FLNA gene, variant:

At cDNA level: NM_00110556.1: c.7922C> T,

At the protein level: p. (Pro2641Leu)

The younger sister did not consent to genetic diagnostics.

Results: Based on clinical observations, we have not yet found the cause of such a different clinical response in sisters suffering from epilepsy and grey matter heterotopia. In our database of patients with epilepsy and grey matter heterotopia, we find cases of good response to treatment, but we do not have siblings with such extremely different clinical manifestations. This provides the basis for further research and close monitoring of these patients.

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Adults with Lennox-Gastaut Syndrome (LGS) have improved everyday executive functioning (EF) with fenfluramine (Fintepla®)

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Purpose: Most adults with LGS experience profound intellectual disability, often leading to institutionalization. Patients with LGS aged 5-18 years showed improvement in EF after 14 weeks of fenfluramine treatment, but the impact on patients initiating treatment in adulthood needs to be evaluated. Here, we evaluate EF in adults with LGS after treatment with fenfluramine in a 14-week randomized clinical trial.

Method: Adult patients with LGS received placebo or fenfluramine (0.2 or 0.7mg/kg/day) for 14 weeks. EF was evaluated at baseline and Week 14 for patients aged 19-35 years with the Behavior Rating Inventory of Executive Function®—Adult Version (BRIEF®-A: Behavioral Regulation Index, BRI; Metacognition Index, MI; Global Executive Composite, GEC). The threshold for clinically meaningful improvement in BRIEF®-A indexes/composite T-scores from baseline to Week 14 was defined as a Reliable Change Index (RCI) of ≥95% certainty; worsening was defined by RCI ≥80%. Clinically meaningful change was evaluated using Somers’ D (p≤0.05).

Results: Data were analyzed for 57 adult patients (placebo, n=23; fenfluramine, n=34; median age, 23 years; 63% male). Median baseline T-scores were clinically elevated across treatment groups (T≥65) for 44% of patients in BRI, 61% in MI, and 60% in GEC. Clinically meaningful improvement at RCI≥95% certainty was observed in BRI (placebo: 1/23, 4.3%; fenfluramine: 8/34, 23.5%; p=0.024), MI (placebo: 1/23, 4.3%; fenfluramine: 9/34, 26.5%; p=0.012), and GEC (placebo: 2/23, 8.7%; fenfluramine: 11/34, 32.4%; p=0.018). No significant or clinically meaningful worsening was observed in any index at RCI≥80%.

Conclusion: Adults with LGS and a high degree of baseline EF impairment showed improvements in EF over a relatively short, 14-week treatment duration. These data suggest that treatment with fenfluramine, even late in neurodevelopment, confers benefits in EF. Further investigation is warranted to determine the longer-term treatment impact of fenfluramine on EF in LGS.

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Basic science

9 Development of behavioral patterns in young Scn1a haploinsufficient mice

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Purpose: Dravet syndrome (DS) is a rare, refractory, infancy-onset epileptic encephalopathy associated with a high premature mortality. DS is typically caused by a heterozygous loss-of-function mutation in the SCN1A gene. Besides the burden of the seizures, pediatric patients suffer from multiple behavioral and cognitive impairments, and struggle with pronounced developmental delays. However, there is only scarce knowledge on behavioral alterations in genetic mouse models of DS over the course of the adolescence phase.

Method: We applied a range of behavioral paradigms suitable for assessment of severity in young mice, and closely monitored the extent of behavioral variations in the Scn1a-A1783V mouse model (n=20) and their wildtype littermates (n=20) during the stages of murine adolescence:
1) prepubescence,
2) pubescence,
3) sexual maturity.

Results: We identified a range of genotype-dependent behavioral characteristics during the developmental course of the animals. Dravet mice displayed a reduced preference for sweetness once they had reached sexual maturity. We observed that nest building behavior was already impacted by genotype from prepubescence onwards. When exposed to the open field test, Dravet mice of both sexes showed pronounced hyperactivity and increased levels of thigmotaxis during prepubescence and once sexually mature. Analysis of Irwin scores revealed genotype- and age-dependent alterations of handling-associated parameters. We detected increased levels of adrenocortical activity in female prepubescent Dravet mice.

Conclusion: In light of the complex clinical phenotype and course, it is of interest that behavioral patterns in young Scn1a haploinsufficient mice recapitulate relevant phenotypical features of DS. The information obtained confirms face validity in the genetic Scn1a-A1783V mouse model, and provides a basis for future studies comparing the consequences of early versus late therapeutic intervention. Moreover, the data provide information about cumulative severity in the model.

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71 Sexually dimorphic microRNAs dysregulation in neonatal recurrent seizure models

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Purpose: Neonatal seizures (NS) are the most common neurological events occurring in newborns affecting approximately 0.3% of infants. Although these seizures dissipate with the age, they often lead to the development of neuropsychiatric conditions, and in some cases initiate epilepsy. The frequency of NS is higher in males than in females. This study aimed to address how sex influences the microRNAs dysregulation in the neonatal recurrent seizure model. Exploring the sexually dimorphic differential expression of microRNAs in animals experiencing neonatal recurrent seizures may provide a novel insight into the NS-related pathophysiology.

Methodology: Rats (n=30; M/F=15/15) were subjected to flurothyl-induced repeated generalized tonic-clonic seizures (n = 5) for 5 consecutive days starting at postnatal day (P) 7. Animals of the same age and sex were used as controls (n=30). Hippocampal tissues were harvested and snap-frozen, 24 hours, 7 days, and 3 months after the last seizure. Total RNA was isolated from the frozen tissues and subjected to massive parallel sequencing (Illumina).

Result: Sequencing analysis showed a distinct miRNA dysregulation at 24hours (16 & 9 miRs), 7 days (10 & 12 miRs), and 3 months (10 & 12 miRs) after the last flurothyl-induced seizure for both male and female animals, respectively. Out of the total dysregulated miRNAs, 4 miRNAs (miR-484, -9a-5p, -383, -665) were commonly dysregulated at the first two time points in both the sexes. miR-484 showed a similar dysregulation pattern. Whereas miR-9a-5p, -383, and -665 showed opposite dysregulation patterns. About 94% of miRNAs dysregulated after NS differed between sexes.

Conclusion: We identified miRNA expression profiles in male and female rat brains across the period following neonatal recurrent seizure until adulthood. Our results indicate sex-related differential expression of miRNAs induced by neonatal seizures.

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Effects of structurally related antiepileptic drugs of the dibenzazepine family on human Na$_{\text{v}}$1.2 sodium channels

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**Purpose:** Voltage-gated Na$^+$ channels are the main therapeutic targets of antiepileptic drugs (AEDs). Among the human Na$^+$ channel isoforms, the Na$_{\text{v}}$1.2 is particularly important because it is a dominant isoform in excitatory neurons. Moreover, gain-of-function mutations in the SCN2A gene cause epilepsy. The effects of the structurally related AEDs of the dibenzazepine family carbamazepine (CBZ), oxcarbazepine (OXC), and eslicarbazepine acetate (ESL) are generally thought to be similar, but a side-by-side comparison in a controlled system is lacking.

**Methods:** Whole-cell patch-clamp recordings were carried out from HEK 293 cells stably expressing SCN2A gene. We evaluated activation and inactivation, and recovery from fast inactivation with standard protocols for the different AEDs (100 µM; CBZ n = 10, OXC n = 9, ESL n = 7).

**Results:** There were significant shifts of steady-state activation and inactivation in all AEDs. CBZ induced a significantly larger shift of the half-maximal steady-state inactivation than OXC and ESL (CBZ vs. OXC $p = 0.027$, CBZ vs. ESL $p = 0.011$, Tukey’s multiple comparisons test). Slowing of the recovery from fast inactivation was significantly more pronounced for CBZ compared to OXC and ESL (CBZ vs. OXC $p = 0.013$, CBZ vs. ESL $p = 0.002$, Tukey’s multiple comparisons test). The reduction of use-dependent block of Na$^+$ channel by OXC was larger than by ESL (OXC vs. ESL $p = 0.018$, Tukey’s multiple comparisons test).

**Conclusion:** OXC and ESL are structurally similar to CBZ, but have quantitatively different effects on voltage-gated fast inactivation and recovery from fast inactivation compared to CBZ. To clarify drug actions on individual sodium channel isoforms will be important in understanding similarities and differences in the mechanism of action of closely related AEDs.

Preexistent gut microbiome profiles determine the risk of post-traumatic epilepsy

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**Purpose:** Traumatic brain injury (TBI) modifies gut microbiome, and these modifications may in turn contribute to TBI sequela. We examined whether post-traumatic epilepsy (PTE) was associated with TBI-induced microbiome perturbations, and/or with preexistent gut microbiome profiles.

**Method:** Adult Sprague-Dawley rats underwent Lateral Fluid Percussion Injury (LFPI). PTE was examined 7 months later via 4-week video-EEG monitoring. 16S ribosomal ribonucleic acid gene sequencing was performed in fecal samples collected before LFPI/sham-LFPI and 1 week, 1 and 7 months thereafter. Bioinformatics included the analysis of alpha and beta diversities, and differential microbial abundances. Short Chain Fatty Acids (SCFA) were measured by Liquid Chromatography with Tandem Mass Spectrometry in fecal samples collected before LFPI.

**Results:** Alpha diversity changed over time in both LFPI and sham-LFPI subjects; no association was observed between alpha diversity and LFPI, the severity of post-LFPI neuromotor impairments, and PTE. LFPI produced significant changes in beta diversity and selective changes in microbial abundances associated with the severity of neuromotor impairments. No association between LFPI-dependent microbial perturbations and PTE was detected. PTE was associated with beta diversity irrespective of timepoint vis-à-vis LFPI, including at baseline. Preexistent fecal microbial abundances of four amplicon sequence variants belonging to the Lachnospiraceae family (three enriched and one depleted) predicted the risk of PTE with area under the curve (AUC) of 0.73. Global SCFA content was associated with the increased risk of PTE with AUC of 0.72. When the analyses of baseline microbial and SCFA compositions were combined, AUC to predict PTE increased to 0.78.

**Conclusion:** While LFPI does not produce microbial perturbations that are specific for PTE, the risk of PTE can be stratified from preexistent microbial abundances and SCFA content. Hence, preexistent microbiome profiling can be used as an early biomarker of PTE.
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Semi-supervised classification of iEEG using temporal autoencoder neural network

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The visual review and interpretation of electrophysiology recordings is a time-consuming and challenging task subject to human operator variability and bias. This challenge has only grown with the emergence of large-scale electrophysiology recordings with high channel counts spanning long time scales. This research presents a semi-supervised deep learning method that utilizes temporal autoencoders to classify iEEG data into four distinct groups (i.e., physiological, pathological, movement & muscle artifacts, power line noise). The model was trained on publicly available datasets consisting of 3-second iEEG clips originating from 14 and 25 patients with drug-resistant epilepsy from two hospitals. Each dataset consists of at least 150 thousand annotated clips.

In general, the semisupervised technique utilizes a small amount of gold standard labeled data and large numbers of unlabelled data to capture underlying patterns in the data. The temporal autoencoders projects iEEG data into low-dimensional embedding space, where data can be efficiently clustered or classified. The classification method utilizes kernel density estimation (KDE) and a naive Bayesian classifier, which process low dimensional embeddings from temporal autoencoder. We believe that this method might be efficiently used to preprocess long-term recordings, where visual inspection of the small amount of data might be easily extrapolated onto the whole recording, which significantly speeds up the iEEG revision. Once the entire recording is analyzed with the autoencoder, the signals segments of interest might be selected and presented to the physicians for further analysis and quantification. Our findings principally support the utility of the semi-supervised method for the training of classifiers on large EEG datasets, where only a minor portion of the data has standard gold labels. Numerical results show that the proposed semi-supervised method archives classification F1-score of 0.7 on hidden testing set while using only one thousand gold standard samples from each classification category.

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Apnoeas and bradyarrhythmias during spontaneous tonic-clonic seizures in rats with hippocampal epileptic foci

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Purpose: We aim to discover the impact of repeated seizures on cardiac and respiratory function in a rat model of temporal lobe epilepsy. The relationship between seizures and cardiorespiratory function may shed light on mechanisms for SUDEP (sudden unexplained death in epilepsy).

Method: Adult rats received an injection of tetanus toxin (List Biological Inc, 25 ng in 250 nl) into one ventral hippocampus. During the same aseptic surgery under general anaesthesia, we implanted an intranasal thermocouple, subcutaneous ECG leads, and electrodes in the ipsilateral (to the injection) dorsal hippocampus and/or neocortex over the contralateral dorsal hippocampus. All sensors connected to a socket cemented to the skull. After recovery from anaesthesia, continuous video-EEG recordings were made through a purpose-built preamplifier (Digitimer Ltd), wires and counterbalanced slip rings, and digitized by a 1401 signal acquisition system running SPIKE2 (CED Ltd).

Results: Once the focus established (3-10 days after injection), time-limited seizures lasting up to 2 minutes occurred spontaneously, typically in clusters lasting a few days. Tonic-clonic phases of seizures were reliably associated with apnoeas lasting a median of 14 seconds (interquartile range 11 to 17 seconds), in a sample of 109 seizures from 6 rats. These apnoeas were associated with bradyarrhythmias of similar durations, as we reported previously (DOI: 10.1111/epi.16479). In the new series we also found cases of premature ventricular contraction during tonic-clonic seizures.

Conclusion: We developed a reliable means of monitoring respiratory airflow together with cardiac and neural electrophysiology in chronically epileptic rats. We found that the convulsive (tonic-clonic) component of seizures led to cessation of breathing, in parallel with cardiac dysfunction as reported previously. These results demonstrate a link between forebrain seizure activity and respiratory and cardiac dysfunction.
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Chronic iEEG recordings and interictal spike rate reveal multiscale temporal modulations in seizure states

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Purpose: In focal epilepsy, various seizure features, such as spread and duration, can change from one seizure to the next within the same patient. In presurgical recordings, within-patient seizure evolutions do not change randomly over time, but instead appear to fluctuate over circadian and slower timescales. The specific timescales of this variability, as well as the seizure characteristics that change over time, are unclear.

Methods: Here we analysed variability in seizure evolutions, which we described as sequences of a finite number of functional network states, in 10 patients with chronic intracranial EEG recordings (185-767 days of recording time, 57-452 analysed seizures/patient). We then compared seizure state occurrence and seizure state duration to (1) time since implantation and (2) patient-specific circadian and multidien cycles in interictal spike rate, which were extracted using empirical mode decomposition.

Results: In most patient, the occurrence or duration of at least one state was associated with the time since implantation (8 and 9 patients for state occurrence and state duration, respectively). Additionally, some patients also had one or more states that were associated with phases of circadian and/or multidien spike rate cycles (4 and 6 patients for state occurrence and state duration, respectively). A given seizure state’s occurrence and duration were usually not associated with the same timescale.

Conclusion: Our results suggest that time-varying factors modulate within-patient seizure evolutions over multiple timescales, with separate processes modulating a seizure state’s occurrence and duration. These findings provide new insight into the patterns and mechanisms of intra-patient seizure variability, with potential implications for forecasting and treating seizures.

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Sulforaphane ameliorates metabolic changes associated with status epilepticus in immature rats

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Purpose: Status epilepticus (SE) is a common paediatric emergency with the highest incidence in the neonatal period and is a well-known epileptogenic insult. As previously established in various experimental and human studies, SE induces long-term alterations in brain metabolism, which contribute to the development of epilepsy. To influence these changes, sulforaphane (SFN) has been used in the present study for its known effect of enhancing antioxidative, cytoprotective, and metabolic cellular properties.

Method: We have used a model of acquired epilepsy induced by LiCl Pilocarpine in immature rats (12 days old). Energy metabolites PCr, ATP, glucose, glycogen, and lactate were determined by enzymatic fluorimetric methods during the acute phase of status epilepticus. Protein expression was evaluated by Western blot analysis. Neuronal death was scored on FluoroJadeB staining 24h after SE. To assess the effect of SFN on glucose metabolism we have performed series of FDG-PET recordings 1h, 1 day, and 3 weeks after the SE. Responses of CBF to electrical stimulation and their influencing by SFN were evaluated by LDF.

Results: We have demonstrated that the Nrf2 pathway is upregulated in the CNS of immature rats after SFN treatment. In the animals who had undergone SE, SFN was responsible for lowering glucose uptake in most regions 1 hour after the induction of SE, reversed hypometabolism observed after 24 hours and achieved full reversal ~3 weeks after SE. No difference in cell death was observed in SFN treated group. SFN per se did not affect the glucose uptake at any given time point. Furthermore, we had discovered that SFN improves blood flow and accelerates CBF response to electrical stimulation.

Conclusion: The present findings suggest that SFN may act as a potential disease-modifying drug influencing metabolic changes induced by SE.

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Neurofilament light chain in the interstitial fluid of the mouse brain, a novel biomarker for epilepsy?

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Purpose: In the management of neurological diseases, there is a compelling need for reliable biomarkers that can improve the prognostic assessment as well as predict the response to treatments. According to the World Health Organization, ± 5 million people are diagnosed with epilepsy each year. Current drugs affect seizures, but no disease-modifying drugs are available that prevent or slow down epileptogenesis, emphasizing the need for new insights in the field. The interest in neurofilaments, especially the neurofilament light chain (NfL) subunit, and their role as neuronal disease biomarkers has grown tremendously in the last decades. NfL is a protein located in the neuronal cytoskeleton and released into the interstitial fluid (ISF) of the brain upon axonal injury and neurodegeneration. The aim of this study is to assess NfL levels in the intrahippocampal kainic acid (IHKA) mouse model for temporal lobe epilepsy.

Methods: To date, no methods have been described that permit analysis of ISF NfL. To this end, we implemented cerebral open flow microperfusion (cOFM) to sample ISF NfL in freely moving C57BL/6J mice before and during status epilepticus (SE) and before and during the spontaneous recurrent seizure phase. cOFM probes are implanted in the ventral hippocampus. SE is induced by unilateral dorsal IHKA injection. The use of both a single molecule array and enzyme-linked immunosorbent assay was explored for sample analysis.

Results: Feasibility to sample ISF NfL using cOFM was first verified. Basal ISF NfL levels of 10-12-week C57Bl/6J mice are 3.02 ± 0.32 ng/mL (n = 5). IHKA experiments are currently ongoing. Preliminary results suggest that ISF NfL levels tend to increase during SE but not during the chronic phase with spontaneous recurrent seizures.

Conclusion: Assessment of the ISF pool of NfL may provide unique insights into the various phases of the IHKA disease model for temporal lobe epilepsy.

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Structural and molecular characterization of the gut-brain axis in a rat model of acquired epilepsy

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Purpose: A dysfunctional gut-brain axis is emerging as a novel pathogenic mechanism in epilepsy but the underlying mechanisms are unknown. Inflammation may affect both intestinal barrier and blood-brain barrier permeability thereby contributing to impair the physiological gut-brain cross-talk. Using a rat model of focal onset epilepsy, we studied whether inflammation occurs in the gut of epileptic animals, thus mirroring the brain phenomenon. We also studied specific gut structural changes that are associated with intestinal dysfunction.

Method: We used a model of status epilepticus (SE)-induced epilepsy provoked by intra-amygdala kainate in 13 days-old male rats. Longitudinal EEG monitoring showed that ~65% of adult rats developed epilepsy (EPI) while the remaining rats did not show spontaneous seizures (no-EPI). At the end of EEG recordings (5 months post-SE), experimental rats and saline-injected sham controls were killed and their intestine was analyzed. Inflammatory markers were measured in the gut by immunohistochemistry (n=6-8) and by RT-qPCR (n=9-13). Quantitative histopathological analysis of gut’s structure was performed in hematoxylin-eosin-stained sections (n=9-13).

Results: Microglia/macrophage Iba1-immunostaining was increased in the duodenum and jejunum of EPI rats vs both controls and no-EPI rats (p<0.01) while astroglia GFAP-immunostaining was similar in all groups. RT-qPCR analysis of glia markers confirmed immunohistochemical data and showed that TLR4 expression was higher in EPI vs no-EPI rats in the duodenum (p<0.05). In the duodenum, villus height/crypt depth ratio and goblet cell number were reduced in EPI rats vs both controls and no-EPI rats (p<0.01). Villus height in the duodenum and jejunum and crypt depth in jejunum were increased in no-EPI rats vs controls (p<0.01) while they did not change in EPI rats.

Conclusion: Epileptic animals showed specific structural, cellular and molecular gut alterations reflecting a dysfunctional inflammatory state. Gut-based therapies should be tested to evaluate their impact on gut dysfunction and seizures.

Acknowledgments: AICE-FIRE
**Purpose:** A circuitry has been previously shown between basal ganglia which includes inhibitory GABAergic and dopaminergic neurons in substantia nigra and cortex which includes excitatory glutamatergic neurons. mGLU2/3 receptors, located extrasynaptically in basal ganglia and limbic structures, have been a prominent target in the treatment of epilepsy. We aimed to evaluate the glutamatergic immunoreactivity in the somatosensory cortex following nigrostriatal dopaminergic pathway degeneration in 90-day-old Genetic Absence Epilepsy Rats from Strasbourg (GAERS) and non-epileptic Wistar rats. Here we described the effects of dopaminergic degeneration on excitatory neurons in the somatosensory cortex.

**Method:** A chemical lesion in the nigrostriatal dopaminergic pathway was induced by 6-hydroxydopamine (6-OHDA) administration into the medial forebrain bundle (AP: -1.4, ML:1.6, V:7.1) of 30-day-old GAERS (n=4) and Wistar rats (n=4) by using stereotaxic surgery. Two different control groups, sham and naive (both group n=4), were used for both strains. The brains were removed following transcardiac perfusion with 10% neutral buffered formalin under deep anesthesia. Thereafter, 40 µm coronal sections were immunohistochemically stained by metabolic glutamate receptor 2 (mGluR2). Glutamatergic immunoreactivity was evaluated by counting of the labeled neurons in the somatosensory cortex region. Brain sections were photographed with Olympus DP72 microscope (Tokyo, Japan) and glutamatergic neurons were counted with ImageJ software (USA). Data were expressed as mean±standard error of mean. Differences between groups were analyzed by one-way ANOVA using GraphPad Prism.

**Result:** There was no significant difference when the 6-OHDA lesioned animals were compared with the control groups in terms of glutamatergic immunoreactivity in the somatosensory cortex.

**Conclusion:** This result shows that nigrostriatal dopaminergic pathway degeneration does not affect glutamatergic immunoreactivity in the somatosensory cortex. We think that our study will contribute to the current literature. The study is funded by the Scientific and Technological Research Council of Turkey, Project number: TUBITAK-SBAG-218S653

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**Histological and electrophysiological correlates of posttraumatic spike-wave discharges in rats**

**Purpose:** To evaluate neocortical spike-wave discharge (SWD) occurrence at baseline (before craniotomy) and in the early post-traumatic period in rats; to assess the role of subcortical structures (thalamus and hippocampus) in neocortical posttraumatic SWDs generation and spreading; to analyze histological correlates of SWDs in the acute period of TBI.

**Methods:** The experiments were performed on 36 adult male Sprague-Dawley rats. In 24 rats ECoG recordings (frontal and occipital cortex) were performed for 7 days before and after lateral fluid percussion brain injury (n=17) or sham-operation (n=7). In 12 rats local field potentials (frontal cortex, ventro-postero-lateral nucleus of the thalamus, dentate gyrus of the hippocampus) were recorded for 7 days before and after TBI (n=7) or sham-operation (n=5). SWD occurrence, waveform, spreading across the cortex and subcortical structures were analyzed together with their histological correlates.

**Results:** One week after TBI the group of animals was significantly heterogeneous regarding the incidence of bifrontal 7-Hz SWDs. We found that 17% of rats had constantly high both baseline and post-craniotomy SWD occurrence (idiopathic SWDs); 50% of rats had low baseline but high SWD occurrence after TBI (posttraumatic SWDs). All SWDs were associated with sleep phases. We revealed associations between the posttraumatic etiology of SWDs and their waveform, bilateral distribution of SWDs in the neocortex and involvement of the thalamus (as compared to idiopathic SWDs). The incidence of posttraumatic SWDs positively correlated with the area of glial activation in the neocortex, and number of neurons with ischemic morphology in hippocampal dentate gyrus.

**Conclusion:** The results show involvement of cortico-thalamo-cortical neuronal network in posttraumatic SWDs generation and its bilateral spreading. SWDs may be involved in posttraumatic epileptogenesis in rat TBI model.

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Changes of chloride cotransporters in mesial temporal lobe epilepsy patients

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Purpose: Epileptogenesis is associated with an excitatory-inhibitory imbalance. And especially epileptogenesis results from a deficit of GABA inhibition. Na-K-2Cl cotransporter isoform 1 (NKCC1) and the K-Cl cotransporter isoform 2 (KCC2) are two main cation-chloride cotransporters. We evaluate the changes of NKCC1 and KCC2 in mesial temporal lobe epilepsy (MTLE) patients.

Method: Human tissues were obtained from 12 patients who underwent epilepsy surgery. Eight patients were diagnosed clinically as TLE with HS and 4 patients who had no evidence of neuronal loss or gliosis were used as normal condition. The hippocampal findings in all cases were confirmed by pre-operative MRI, and histological pathology was examined by independent neuropathologists after epileptic surgery. The brain tissues were deparaffinized and processed for labeling with NKCC1 and KCC2 antibodies as previously described Immunocytochemistry method.

Results: NKCC1 was increased in CA1 and CA3 in MTLE patients compared with control. But KCC2 was decreased in whole hippocampal area including CA2 in MTLE patients.

Conclusion: Increase of NKCC1 and decrease of KCC2 contribute to the epileptogenesis by diminish the efficacy of GABA receptor inhibition. NKCC1 and KCC2 to be therapeutic targets for the development of new mechanism antiepileptic drugs.

Sleep and temperature dysregulation in a mouse model of Dravet syndrome

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Background: Dravet syndrome (Dravet) is a rare, severe developmental epileptic encephalopathy (DEE). Most cases of Dravet are caused by loss of function mutations in the SCN1A gene, which encodes a voltage-gated sodium channel NaV1.1. More than 70% of Dravet patients experience sleep disturbances, with difficulties initiating sleep and problems in sleep-wake transitions. Furthermore, temperature deficits are common in Dravet, with reduced sweating and intolerance of cold.

Method: We performed electrocorticogram (ECoG) recordings concomitant with body core temperature measurements during wakefulness and non-REM (NREM) sleep in WT and Dravet mice at the onset of severe spontaneous seizures.

Results: Power spectral analysis of background EEG activity demonstrated a marked reduction in power spectral density during both wakefulness and sleep in Dravet mice. Importantly, the power was lower in mice that died prematurely. Moreover, while transitions to NREM sleep were always associated with a reduction in core body temperature in WT mice, recordings of Dravet mice revealed difficulties in maintaining low temperatures which are necessary for good sleep quality. To further explore the basis of dysregulation of sleep temperature we performed depth recordings from the hypothalamic ventrolateral preoptic nucleus (VLPO) area and the locus coeruleus.

Conclusions: Together, our data demonstrate sleep and temperature dysregulation in Dravet mice. In addition to mechanistic insights into these deficits, our data imply that long-term EEG monitoring with simultaneous continuous monitoring of body core temperature can be used as a diagnostic tool for Dravet.
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**Targeting the Sigma-1 protein: efficacy of the positive Sigma-1 modulator E1R in the amygdala kindling model of temporal lobe epilepsy**

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**Purpose:** Fenfluramine is licensed in Europe as an add-on treatment option for patients with Dravet syndrome. Fenfluramine interacts with the serotonergic system and a positive modulation of Sigma-1 is discussed. The relative contribution of fenfluramine’s interaction with Sigma-1 to its anticonvulsant effects is still unknown. For direct comparison, we assessed the effects of the selective positive allosteric Sigma-1 modulator methylphenylpiracetam (E1R) in the amygdala kindling model.

**Method:** Female NMRI mice (n=23) were electrically stimulated once daily until they developed ten generalized seizures. The effects of E1R, the Sigma-1 antagonist NE-100 and their combination were determined in fully-kindled mice (n=16; i.p.; vehicle: 0.9% saline; E1R: 25/50/75/100 mg/kg; NE-100: 5/25 mg/kg; combination NE-100/E1R: 25/50/50 mg/kg). Pretreatment times of 60 minutes for E1R and 80 minutes for NE-100 were applied. The impact on seizure thresholds and seizure parameters was assessed in comparison to preceding vehicle-control trials. Tolerability was analysed based on the rotarod test and a subset of Irwin score parameters.

**Results:** E1R dose-dependently increased seizure thresholds, and reduced seizure severity, seizure and afterdischarge duration at threshold stimulation. An effective dose 50 (ED₅₀) of 35.25 mg/kg was determined for the impact on generalized seizure thresholds (GST). Rotarod test and the selected Irwin score parameters indicated that E1R is well tolerated even at higher doses (100 mg/kg). Pretreatment with NE-100 decreased the effects of E1R on GST (p=0.0273) when compared to E1R treatment alone.

**Conclusion:** Our findings indicate that positive modulation of Sigma-1 exerts anticonvulsant effects with an impact on seizure generation, spread of seizure activity, and seizure termination. Thus, Sigma-1 may be suitable as a potential target for epilepsy therapy.

In follow-up experiments, we will determine the ED₅₀ of fenfluramine in the kindling model and the relevance of its interaction with Sigma-1.

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**Long-term outcomes and disease progression in an infantile rat model of acquired epilepsy**

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**Purpose:** Paediatric status epilepticus (SE) may result from acquired, metabolic, immune, genetic or unknown causes and often leads to neurological sequelae, including epilepsy. Epicileptic activity itself in children may contribute to disease progression beyond what is expected by the underlying pathology. We characterized in-depth an infantile rat model of SE-induced epilepsy to provide a means to study the encephalopathic effects of seizures, the underlying pathogenic mechanisms and new biomarkers and treatments.

**Method:** SE was induced in video-EEG monitored 13-day old male rats by intra-amygdala kainate injection (KA, 2 μg/0.2 μl, n=83). Sham animals were similarly injected with saline (n=33). Glia activation and Fluoro-Jade-positive neurons were analyzed in forebrain by (immuno)histochemistry (n=6) and neuroinflammation/oxidative stress were measured in the hippocampus by RT-qPCR (n=7-12). ECoG was performed post-SE to detect spontaneous seizures. Rats were tested in the Morris Water Maze to evaluate their cognitive status. A sub-group of rats was analyzed longitudinally by 7T MRI (n=24).

**Results:** Convulsive SE developed 31.0 ± 2.3 min after KA injection and elapsed within 3.5 ± 0.5 h. Spontaneous seizures occurred in ~60% of animals as assessed by 2 weeks (24/7) ECoG recordings at 1.5 months (0.3 ± 0.3 seizure/day), and daily seizures significantly (p<0.05) increased to 1.1 ± 0.6 seizure/day at 5 months post-SE. Neuroinflammation, oxidative stress, reactive gliosis occurred in forebrain during the first week post-SE. Hippocampal neurodegeneration was bilateral in rats developing epilepsy while it was unilateral to the injected amygdala in non-epileptic rats. Epileptic rats also displayed progressive cognitive deficits 12 days to 2 months post-SE whereas non-epileptic rats performed similarly to shams. Diffusion tensor imaging metrics significantly correlated with seizure frequency and cognitive deficits in epileptic rats.

**Conclusions:** This model reproduces salient features of encephalopathic effects of seizures in early life. It is useful for mechanistic and biomarker studies and for testing disease-modifying drugs.
Regeneration in 60- and 90-day old genetic absence epilepsy rats induced by the 6-hydroxydopamine in the medial forebrain bundle

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Purpose: The development of epilepsy depends on a number of neurobiological processes called epileptogenesis. Limited number of studies have shown that cortex and thalamus that play role in the pathophysiology of epilepsy, are affected during epileptogenesis. Here we aimed to determine the effect of degeneration of nigrostrial dopaminergic pathway on the dopaminergic immunoreactivity of striatum in Genetic Absence Epilepsy Rats from Strasbourg (GAERS) in two different ages (60 and 90 days old).

Method: A chemical lesion was induced by 6-hydroxydopamine (6-OHDA) administration to the medial forebrain bundle (MFB) (AP:-1.4, ML:1.6, V:7.1) of the 30-day-old GAERS using stereotaxic surgery. When the first group was 60-day-old (n=6) and the second group was 90-day-old (n=5), the brains of the animals were perfused with 10% neutral buffered formalin and then removed. Forty µm coronal sections were used for tyrosine hydroxylase immunohistochemical staining. For each group, photomicrographs were captured via Olympus-DP72 microscope (Tokyo, Japan) and dopaminergic immunoreactivity in the striatum was calculated by densitometric analysis (ImageJ Software, USA). The data was expressed with t-test as mean±standard error of mean and analyzed by Graphpad Prism.

Results: When dopaminergic immunoreactivity in the striatum of the 60- and 90-day old GAERS was compared, the dopaminergic degeneration was statistically more pronounced in the 60-day old group(44.45±5.26) when compared to the 90-day-old GAERS(64.18±5.86).

Conclusion: This study suggests a regeneration in striatum over time after 6-OHDA-induced degeneration in GAERS. This brings to mind the question of whether the regeneration after 6-OHDA injection occurs in Wistar rats that have healthy genetic background. In our further studies, we aim to find an answer to this. When the literature was examined, no study was found investigating the striatal degeneration following 6-OHDA induced MFB lesion regarding the age difference of animals. This study funded by the Scientific and Technological Research Council of Turkey, TUBITAK-SBAG-218S653.

Evaluation of the activity of dopaminergic neurons in ventral tegmental area in rats after 6-hydroxydopamine injection

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Purpose: There are studies showing a positive correlation between epileptic activity in absence epilepsy and dopaminergic neuron density in substantia nigra. It is known that dopaminergic neurons also exist in the ventral tegmental area (VTA). The effect of 6-hydroxydopamine (6-OHDA) induced nigrostrial pathway degeneration on dopaminergic immunoreactivity (ir) of the VTA was examined in Genetic Absence Epilepsy Rats from Strasbourg (GAERS) and non-epileptic Wistar rats.

Method: A chemical lesion was induced by 6-hydroxydopamine (6-OHDA) administration to the medial forebrain bundle in the GAERS (n=4) and Wistar rats (n=4). Naive GAERS and Wistar rats were used as control. The brains were removed following transcardiac perfusion under deep anesthesia. Forty µm coronal sections were immunohistochemically stained by tyrosine hydroxylase. Olympus-DP72 microscope was used to photograph brain sections. Dopaminergic neurons were evaluated by densitometric analysis (ImageJ software, USA) in ipsilateral and contralateral hemispheres. Data were expressed as mean±standard error of mean.

Results: When dopaminergic-ir in the VTA were assessed, there was no significant difference between naive control groups. In nigrostrial pathway degenerated groups, densitometric analysis showed no difference between 6-OHDA-injected GAERS and Wistar rats in ipsilateral and contralateral hemispheres. When 6-OHDA lesioned animals were compared with their naive animals, no significant difference was found.

Conclusion: Rodrigues et al. (International journal of neuroscience, 2004, 114(2), 197-216) found a significant difference between both hemispheres in terms of dopaminergic-ir in the VTA after 8 µg 6-OHDA injection to the striatum in Wistar rats. We will examine the dopaminergic-ir in the VTA after the 6-OHDA injection applied to the striatum region in our further studies. This study will contribute to the literature since there are few studies on the VTA in GAERS. This study was funded by Scientific and Technological Research Council of Turkey(TUBITAK-SBAG-218S653). First author is The Council of Higher Education (YÖK) 100/2000-PhD scholar.
Association of autonomic nervous functions, peripheral nervous functions and insulin resistance in recently diagnosed type 2 diabetes mellitus

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**Purpose:** Insulin resistance (IR) and hyperglycaemia in long-standing type 2 diabetes mellitus (DM) are associated with many microvascular complications resulting in neuropathy, nephropathy etc. In recently diagnosed patients with DM the overt symptoms of neuropathy are usually absent. However, affection of nerves (autonomic and peripheral) is one of the major complications of long-standing DM and causes significant morbidity. Therefore, the present study was aimed to explore the associations of insulin resistance, autonomic nervous functions and peripheral nerve conduction velocities, in the patients with recently diagnosed type 2 diabetes mellitus.

**Method:** In 30 recently diagnosed patients with type 2 DM autonomic functions were assessed by heart-rate-variability (HRV), blood-pressure-variability (BPV) and baroreflex-sensitivity (BRS). Peripheral nervous functions were assessed by measuring nerve conduction velocities in peroneal, tibial and sural nerves. Insulin resistance was estimated using the homeostatic model assessment of insulin resistance (HOMA-IR).

**Results:** Significant correlations were observed between nerve conduction velocities of lower limb peripheral nerves and HRV parameters [LF(nu), HF, HF(nu), LF/HF ratio]; BPV parameters [RMSSD, HF, LF/HF ratio of systolic BPV; CV, SENN, LF, HF, LF/HF ratio of mean BPV; CV, SENN of diastolic BPV]; BRS parameters [αHF of systolic and mean BP]. Significant correlations were also observed between HOMA-IR and LF(nu) (r = 0.40; p = 0.028), HF (r = 0.38; p = 0.037), HF(nu) (r = 0.38; p = 0.037), LF/HF ratio (r = 0.47; p = 0.008) of HRV parameters. However, no significant correlations were found between insulin resistance and any of the BRS and BPV parameters.

**Conclusion:** Autonomic functions and peripheral nerve conduction velocities are correlated in the patients of recently diagnosed type 2 DM patients. Insulin resistance is found to be correlated with few parameters of autonomic functions but not with the peripheral nerve conduction velocities.

Hippocampal seizures strongly modulate the activity of locus coeruleus neurons

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**Purpose:** Noradrenaline is associated with predominantly anticonvulsant effects, although evidence suggest that excessive noradrenergic transmission can exacerbate seizures. The locus coeruleus (LC), a deep brainstem nucleus, is the sole source of noradrenaline in large parts of the brain. Previous studies suggest activation of the LC and increased levels of noradrenaline in relation to seizures. In this study, we conduct a detailed assessment of the response of locus coeruleus neurons to acute hippocampal seizures.

**Method:** Male Sprague Dawley rats (n=9) were anesthetized and stereotactically implanted with local field potential electrodes in the dentate gyrus and a stimulation electrode in the perforant path for seizure induction. The activity of LC neurons was measured using 32 channel silicon probes, with or without an optic fiber attached. An optic fiber was used for light delivery in a subset of rats expressing the inhibitory opsins GtACR2 in the LC (n=5 rats).

**Results:** A total of 97 LC neurons were identified on the basis of a burst-inhibition response to noxious stimuli and/or inhibition upon activation of GtACR2 using blue light pulses (3-7 seconds). Hippocampal seizures were associated with strong changes in neuronal firing rates. A total of 54/97 (56%) neurons were significantly inhibited by seizures, 27/97 (28%) neurons were significantly excited by seizures, while 16/97 (16%) neurons showed no significant change. Topographic visualization of multi-unit activity during seizures revealed a tendency for excited and inhibited neuronal activity to be organized in anatomically distinct clusters in multiple animals.

**Conclusion:** Hippocampal seizures, evoked by perforant path stimulation, lead to a mixture of activation and inhibition of locus coeruleus neurons, which appeared organized in anatomically distinct clusters. Future research will determine the role of the observed seizure-related LC response in modulating seizure activity, which is likely to be important to understanding seizure pathophysiology.
Pericardial injection of kainic acid in zebrafish larvae induces spontaneous and chronic epileptic seizures

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Purpose: In rodents, injection of kainic acid (KA) results in the development of spontaneous epileptic seizures, reflecting similar neuropathological characteristics as seen in patients with temporal lobe epilepsy. Although this model has significantly contributed to increased knowledge of epileptogenesis, it is technically demanding and costly to operate, hence not suitable for high-throughput screening of anti-epileptic drugs (AEDs). Zebrafish, a vertebrate with complementary advantages to rodents, is an established animal model for epilepsy research. Here, we established a novel KA-induced epilepsy model in zebrafish larvae that we functionally and pharmacologically validated.

Method: KA was administered by pericardial injection at an early zebrafish larval stage. The induced epileptic phenotype was examined by quantifying seizure behavior and epileptiform discharges by automated video tracking and local field potential (LFP) recordings, respectively. We also assessed GABAergic and glutamatergic neurons in double transgenic KA-treated injected zebrafish larvae, and examined GABA and glutamate levels in the larval heads by liquid chromatography with tandem mass spectrometry detection. Finally, KA-injected larvae were exposed to five commonly used AEDs by immersion for pharmacological characterization.

Results: Shortly after injection, KA induced massive damage and inflammation in the zebrafish larval brain and seizure-like locomotor behavior. After 48 hours, epileptogenic disorganization of the brain was observed, resulting in spontaneous and continuous epileptiform brain activity. Additionally, neuronal cell counts and titration of neurotransmitter levels revealed a decrease in both GABAergic and glutamatergic networks. Three out of five AEDs tested rescued LFP abnormalities but did not affect the seizure-like behavior.

Conclusion: Overall, pericardial injection of KA in zebrafish larvae induces spontaneous recurrent seizures after a short latency period, as seen in rodent models. Hence, for the first time, we describe a chemically-induced larval zebrafish epilepsy model suitable for high-throughput AED screening purposes and rapid genetic investigations.

Higher susceptibility to 6 Hz corneal kindling and lower responsiveness to antiseizure drugs in mouse models of Alzheimer’s disease

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Purpose: Epileptic spikes and seizures seem present early in the disease process of Alzheimer’s disease (AD). However, it is not clear how different forms of soluble and insoluble amyloid beta (Aβ) and tau proteins affect hyperexcitability and epileptogenesis in vivo. We aim to contribute to this field by assessing vulnerability of young mice of two well-characterized transgenic AD models in the 6 Hz corneal kindling paradigm and by testing their responsiveness to selected antiseizure drugs (ASDs).

Method: We used seven-week-old triple transgenic (3xTg) mice that have both amyloid and tau mutations, and APP/PS1 mice, bearing only amyloid mutations. We assessed the absence of plaques via immunohistochemistry and analyzed concentrations of both soluble and insoluble forms of Aβ and total tau (T-tau) in brain hippocampal and prefrontal cortical tissue. Seven-week-old mice of the different genotypes were subjected to the 6 Hz corneal kindling model of epileptogenesis. After kindling acquisition, we tested the anticonvulsant effects of three marketed ASDs (levetiracetam, brivaracetam and lamotrigine) in these fully kindled mice.

Results: No Aβ plaques are present in either genotype. Soluble Aβ levels were increased in both AD genotypes, while insoluble Aβ concentrations were only elevated in APP/PS1 mice compared with their respective controls. Soluble and insoluble forms of T-tau were increased in 3xTg mice only. 3xTg and APP/PS1 mice displayed more severe seizures induced by 6 Hz corneal kindling from the first stimulation onwards and were more rapidly kindled compared with control mice. In fully kindled AD mice, ASDs were less potent against seizures than in fully kindled control mice.

Conclusion: Mutations increasing Aβ only or both Aβ and tau in the brain, enhance susceptibility for seizures and epileptogenesis in mice. The lower potency of ASDs in both investigated AD models demonstrates that seizures of young AD mice are more difficult to treat.
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Modulation of AMPA receptors as therapeutic strategy to counteract neuronal hyperexcitability and cognitive deficits in mouse models of cerebral amyloidosis

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Purpose: Pathological accumulation of Aβ oligomers has been linked to neuronal networks hyperexcitability, potentially underpinned by glutamatergic AMPA receptors (AMPARs) dysfunction. The aim of our work was to investigate if the pharmacological modulation of AMPARs may counteract the alteration of hippocampal epileptic threshold and synaptic plasticity linked to Aβ oligomers accumulation and seizure susceptibility in vivo.

Method: Field- excitatory postsynaptic potentials (fEPSPs) were recorded from hippocampal dentate gyrus area (DG) in an acute model of Aβ induced neurotoxicity. The in vitro models of epileptic-like activity were induced with bath-application of either bicuculline or 4-aminopyridine (4-AP). Long-term potentiation (LTP) was induced by high frequency stimulation. Moreover, seizure susceptibility against bicuculline and 4-AP in an in-vivo model of amyloidosis obtained by stereotaxic injection of Aβ oligomers in the DG was evaluated. Injected mice were also challenged to hippocampal based behavior and cognition with the Morris water maze, passive avoidance and novel object recognition tasks, to assess cognitive deficits associated with oligomers accumulation. Forced swimming test and elevated plus maze were used to study depression and anxiety-like behaviors, respectively. Furthermore, the expression of inflammation-related cytokines, in brain tissue, were measured by ELISA.

Results: Aβ induced in-vitro hyperexcitability was counteracted by AMPARs non-competitive antagonism which, per se, does not affect physiological synaptic transmission. In parallel, the reduced in-vivo epileptic threshold found in Aβ oligomers-injected mice was restored by AMPARs block. AMPARs inhibition also restored Aβ-induced impairment of hippocampal LTP in vitro and significantly improved hippocampal-based cognitive performances of Aβ-lesioned mice. No differences were detected in the forced swimming test and elevated plus maze. Interestingly, AMPARs modulation was able to reduce inflammatory cytokines in this model.

Conclusion: Targeting glutamate AMPARs might be a strategy to reduce hippocampal networks hyperexcitability and synaptic plasticity deficits induced by Aβ oligomers accumulation.

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Seizure susceptibility to various convulsant stimuli in BTBR mouse model of autism spectrum disorders

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Purpose: It is known that 5-30% of individuals with autism spectrum disorder (ASD) have epilepsy. The high co-occurrence of these disorders suggests a common mechanistic link. In here, the susceptibility of BTBR mice, a validated mouse model of ASD, to various convulsant stimuli has been evaluated and compared to C57BL/6J.

Method: BTBR and C57BL/6J mice were administered with chemoconvulsants acting on various brain systems: GABA (bicuculline, picrotoxin, beta-carboline, PTZ); glutamate (AMPA, NMDA and Kainate) or 4-aminopyridine. The convulsants drugs were given by standardized procedures (1). Occurrence of clonic and/or tonic seizures was evaluated to observe possible differences in seizure susceptibility. In another set of mice, protocol chemical kindling was induced by administration of subconvulsant doses of pentylentetrazole (PTZ, 30 mg/kg i.p.) every other day up to kindling development (2).

Results: BTBR mice showed a higher susceptibility to seizures induced by chemoconvulsants impairing the GABA neurotransmission. In contrast, no significant differences in seizure susceptibility were observed after administration of other convulsants. During PTZ kindling, the development of seizures was progressive and directly proportional with the repeated administration of PTZ and the time latency to the first seizure was significantly different between two strains. In particular, BTBR mice exhibited a lower seizure severity and a longer latency in the development of chemical kindling.

Conclusion: The present data suggest that BTBR mice possess an increased susceptibility to some convulsant stimuli while being resistant to kindling development. Further studies are needed to understand which mechanisms are responsible for the observe differences also in term of neuronal network activities.

References:
- De Sarro et al., Neurosci Res. 2004;50:37-44.
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Comparing data- and model-driven approaches to identify epileptic brain states in rat and human electrophysiology

<table>
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<tr>
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**Purpose:** Current advances in epilepsy treatment aim to personalize and responsively adjust treatment parameters to overcome patient heterogeneity and to increase treatment efficiency. These require tools to identify locations and time points of high/increasing seizure likelihood to intervene at the right time and place. Here, we compare model- and data-driven approaches to detect epileptic brain states in local field potentials and intracranial EEG (iEEG).

**Method:** We classify brain states using a set of signal features for each 5 sec segment of data, comparing its feature values against prototypical feature values of four types of activity (interictal, pre-onset, onset, ictal). For data-driven classification (DDC), prototypes are obtained by clustering features of segments of data recorded in rat hippocampal slices. For model-driven classification (MDC), features are clustered from simulations of the Wendling model (J Clin Neurophysiol 2005; 22(5):343–356;) with type-specific model configurations. Classification accuracy is assessed against visual classification for real data or known model configuration for simulated data, across different feature preprocessing versions, first for the classification dataset (“self accuracy”), then for other datasets, including human data from the SWEC-ETHZ iEEG Database.

**Results:** Overall, self accuracy was high (DDC: 77-89%, MDC: 72-99% correct identification), as was the accuracy for classifying real data using MDC (60-81%), and model data using DDC (25-96%). While MDC allowed unambiguous classification for all types of activity, DDC occasionally merged the interictal and pre-onset types. Both strategies identified epileptic states in the human validation dataset (DDC: 68-77%, MDC: 68-70%), with DDC showing slightly better results.

**Conclusion:** Model- and data-driven classification show a great overlap when identifying epileptic brain states in simulated, rat, and human data, indicating similar electrophysiological patterns of epileptic states and a potential for an application to treatment optimization.

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Increased seizure susceptibility and disturbed cognitive performance after intracerebroventricular injections of NMDAR antibody in passive transfer rat model of autoimmune encephalitis

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<th>S Akat Piskin1, H Yuceer2, CA Ulusoy3, CI Kucukali3, F Onat4,5, E Tuzun3, N Carcak Yilmaz1</th>
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**Objective:** N-Methyl-D-Aspartate receptor antibody (NMDAR antibody) encephalitis is a distinct neuro-immunological disorder associated with seizures and cognitive problems. The molecular and neural mechanisms responsible for the development of NMDAR antibody positive autoimmune encephalitis are not fully understood. We aim to develop an in-vivo antibody-mediated autoimmune encephalitis rat model in which serum antibodies (IgG) obtained from blood samples of NMDAR antibody positive encephalitis patients were passively transferred in non-epileptic Wistar rats.

**Material and method:** Total IgG obtained from the sera of NMDAR antibody positive patients and healthy subjects was applied chronically every other day for 11 days into the cerebral lateral ventricle. Spontaneous seizure development was followed by recording cortical electroencephalography (EEG) on consecutive days and after infusion administration. Y-Maze, Open field test and Rota-Rod behavioral tests were applied to the animals before the antibody infusions started and at the end of the infusions. Then, pentylenetetrazole (PTZ) was administered at a convulsive dose (45 mg/kg) intraperitoneally in order to detect possible changes in seizure susceptibility.

**Results:** No spontaneous activity was observed in cortical EEG during and after the antibody infusions administered chronically for 11 days. PTZ-induced seizure stage was significantly higher in the NMDAR antibody group compared in the control (p<0.05). In addition, the number of spontaneous alternating periods and entry into the arms in the Y-maze test significantly decreased in the NMDAR antibody group (p<0.05). Rota-Rod Test results also showed that the NMDAR group had statistically significantly lower values in terms of mean latency compared to healthy controls (p<0.05).

**Conclusions:** These findings provide evidence that NMDAR antibody administration displays seizure susceptibility, disturbed cognitive performance, locomotor activity and motor performance in vivo. The NMDAR antibody-mediated autoimmune encephalitis rat model developed in this study could potentially serve as complementary in-vivo model for anti-NMDAR encephalitis and deserve future investigations.
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Does cannabidiol fail to suppress spontaneous seizures in the intrahippocampal kainic acid mouse model of mesial temporal lobe epilepsy?

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Purpose: Mesial temporal lobe epilepsy is the most common form of focal epilepsy. The therapeutic response to antiseizure drugs is heterogenous and cannot be controlled in two out of three patients. Cannabidiol has been successfully applied to suppress seizures in intractable forms of childhood epilepsy syndromes such as Lennox-Gastaut syndrome and Dravet syndrome. However, evidence on its seizure suppressing potential in temporal lobe epilepsy is sparse. Therefore, this study aims to assess the effect of cannabidiol on the recurrent spontaneous seizures in a mouse model of refractory temporal lobe epilepsy.

Method: C57Bl/6J mice of 8 to 10 weeks of age were unilaterally injected with kainic acid and a depth electrode was implanted in the affected dorsal hippocampus. Using electroencephalographic recordings in freely moving mice, the effect of three different doses of cannabidiol (10mg/kg, 100mg/kg, 200mg/kg) on the occurrence of spontaneous seizures was evaluated and compared to an intraperitoneal injection containing vehicle.

Results: Our preliminary data suggest no significant effect of cannabidiol on seizure frequency or seizure duration compared to a vehicle injection in the intrahippocampal kainic acid model for mesial temporal lobe epilepsy.

Conclusion: Our data suggests that cannabidiol is not able to modify the seizure burden or the duration in the intrahippocampal kainic acid mouse model of mesial temporal lobe epilepsy. Continuation of the study is necessary to confirm the results.

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Quantitative EEG changes during episodes of treatment-refractory status epilepticus in children

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Purpose: Over a third of children presenting with status epilepticus (SE) do not respond to first-line treatment with benzodiazepines. Data from animal models have implicated changes in inhibitory synaptic signalling in this treatment resistance, but their relevance in patients is unknown. This study aims to comprehensively characterise a cohort of paediatric patients with treatment-refractory SE and identify key changes in quantitative EEG features that may in the future act as biomarkers for pathophysiological synaptic changes.

Methods: We retrospectively identified all patients undergoing EEG recording for treatment resistant status epilepticus at the Univeristy Children’s Hospital Zürich, a tertiary referral centre also providing emergency services for the local population. Using time-frequency analysis of spectral changes in the EEG activity, we identify key, time-varying changes associated with failure to respond to treatment.

Results: In our cohort of patients with episodes of treatment-resistant SE (n = 57), we found that in the majority (70%) of SE episodes, patients presented in convulsive SE, which was continuous in nature (60%). The delay to first-line treatment was over 60 minutes in 20% of patients, and in over a third (37%), there was no response to repeated doses of short-acting benzodiazepines. There are frequency band-specific spectral changes that depend on the duration of SE episodes, which may be developed as biomarkers in the future.

Conclusion: Our study identifies key temporal changes in the EEG signature of prolonged SE. Using model-based analysis approaches, we are now able to infer parameters of synaptic pathophysiology from EEG data. In the future, we endeavour to use these types of EEG recordings to study changes in synaptic physiology underlying benzodiazepine-resistance SE.
In vitro effects of brivaracetam in an astrocyte-microglia co-culture model of inflammation

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Purpose: The involvement of astrocytes and microglia in the pathophysiology of epilepsy raises the question how these cells besides neurons may be responsive to current pharmacological treatments. Little is known about direct effects of the antiepileptic drug brivaracetam on glial cells. Therefore, we aimed to study the brivaracetam effects on glial viability, microglial activation, expression of gap-junctional (GJ) protein Connexin 43 (Cx43) as well as intercellular communication in an in vitro astrocyte-microglia co-culture model of inflammation.

Methods: Primary rat astrocytes co-cultures, which contain 5% (M5, mimicking „physiological“ conditions) or 30% (M30, mimicking „pathological inflammatory“ conditions) of microglia, were treated with different concentrations of brivaracetam [0.5, 2, 10 and 20 μg/ml] for 24 h. Glial cell viability was measured by MTT assay. Immunocytochemistry was performed to analyze the microglial activation state and the astroglial Cx43 expression. The GJ cell communication was studied via Scrap Loading.

Results: A concentration-dependent incubation with brivaracetam did not affect the glial cell viability under pathological conditions. However, the glial viability was significantly reduced after incubation with high, overdose concentration (20 μg/ml) of brivaracetam compared to controls and lower, normal concentrations (0.5 and 2 μg/ml) under physiological conditions (p < 0.01: **). Astroglial Cx43 expression was detected under all conditions. A concentration-dependent incubation with brivaracetam did not affect the functional coupling via GJs under inflammatory M30 conditions. Interestingly, incubation with low concentration (0.5 μg/ml) of brivaracetam led to a significant increase of gap-junctional coupling under physiological M5 conditions (p < 0.05: *).

Conclusion: Brivaracetam has not shown effects on the glial cell viability and gap-junctional coupling under inflammatory conditions. However, reduced glial cell viability was detected after treatment of physiological co-cultures with high concentration, suggesting toxic effects by overdose.

Dissecting the contribution of hippocampal and non-hippocampal high frequency oscillations in human memory

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Purpose: High Frequency Oscillations (HFO: 30-180Hz) are associated with normal brain memory function, but also as potential biomarkers of the epileptogenic brain. Here we dissect hippocampal and non-hippocampal HFO during several stages of memory processing: encoding, maintenance and short and long-term retrieval.

Method: HFO were acquired from intracranial recordings from 10 patients (seven males and three females, age 18–51 years) undergoing intracranial seizure monitoring for surgical treatment of epilepsy. The task involved the encoding of sequences of 4 images depicting realistic episodes, their maintenance during 3 sec, their immediate retrieval (i.e., short-term), and a subsequent retrieval the day after encoding (i.e., long-term).

Results: We found hippocampal broadband HFO at encoding and at short and long-term retrieval but not during memory maintenance. Hippocampal broadband HFO did not predict successful memory encoding but distinguished successful memory retrieval (p < 0.05; cluster-based permutation test), especially at long-term. A more narrow-band HFO (50-80Hz) was found in non-hippocampal cortical recordings (i.e., temporal cortex) at encoding and retrieval and were not different between remembered and forgotten episodes.

Conclusion: These findings support an important role for hippocampal HFO in human memory retrieval and extend our understanding of normal physiological brain activity during memory processing.
The third-generation antiepileptic drug, eslicarbazepine improved seizures induced cognitive decline in rats: role of inflammation, oxidative stress, and apoptosis

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Purpose: The complaints of cognitive decline are found to be very frequent in patients with epilepsy and are caused by multiple factors. The aim of the present study was to evaluate the protective effect of eslicarbazepine against cognitive impairment induced by the kindling model of seizures in rats.

Method: The role of inflammation, oxidative stress, and apoptosis was studied in male Wistar rats treated with pentylenetetrazole (30 mg/kg, i.p.) for 28 days. The kindled rats were also administered with eslicarbazepine (100 and 200 mg/kg) orally for 15 days. The seizure scoring was done by Racine scale for 30 mins daily. The cognitive functions were determined by Morris’s water maze, elevated plus maze, and passive avoidance tests. Inflammatory markers like Interleukin-1β, Interleukin-6 & TNF-α, oxidative stress markers like reduced glutathione, malondialdehyde & superoxide dismutase) and apoptotic markers (caspase-1 and 9) were studied.

Results: Pentylenetetrazole treatment produced significant cognitive impairment (p<0.01) and Eslicarbazepine showed dose-dependent protection against cognitive decline (p<0.01) induced by seizures. It has been found that ESL has significant anti-inflammatory (p<0.01), anti-oxidant (p<0.001), and anti-apoptotic (p<0.001) potential by studying its effect on different parameters like oxidative stress, inflammatory markers, and apoptotic markers.

Conclusion: The multiple pathways were found to be involved in cognitive impairment induced by seizures. Moreover, eslicarbazepine (100 and 200 mg/kg) elicits anti-inflammatory, anti-apoptotic, and antioxidant effects for being a treatment option for both epilepsy and Alzheimer’s disease.

The effect of optogenetic activation of hippocampal interneurons on interictal epileptiform discharges

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Purpose: Interictal epileptiform discharges (IEDs) represent a traditional marker of the epileptiform activity. IEDs’ cellular and network mechanisms vary, and various forms were identified. Detailed understanding of the mechanisms involved in IED genesis is crucial for the functional characterization of the epileptic tissue and elucidation of the processes that control seizure emergence. We aimed to dissect the role of somatostatin (SST) and parvalbumin (PV) interneurons in hippocampal IEDs using optogenetics.

Methods: Adult PV-Cre and SST-Cre mice were injected with viral vector pAAV-hChR2(H134R)-mCherry into the hippocampus. After four weeks, the brain was extracted and cut into 350 µm thick sagittal slices. The slices were perfused by artificial cerebrospinal fluid with a high concentration of potassium. The ChR2-transduced interneurons were stimulated by blue light 470 nm wavelength at various light intensities.

Results: IEDs were recorded from CA3 of 12 SST-Cre and 11PV-Cre slices. Optical activation of PV interneurons by 0.5 s pulse suppressed IEDs or reduced the probability of IED occurrence (p<0.05). A rebound increase in IED probability followed the stimulus withdrawal. The activation of SST interneurons induced IED at the onset of the light pulse, followed by a period of IED suppression until the next pulse (p<0.001). We compared the morphological properties of spontaneous and light-induced IEDs and superimposed high-frequency oscillations (HFOs). We found that light stimulation decreases the width of superimposed HFOs by 10±3.4%, p=0.054, Wilcoxon signed-rank test.

Conclusion: We have shown that synchronous activation of PV interneurons can inhibit IEDs. Unexpectedly, the activation of SST interneurons triggered IEDs. This observation could be attributed to the intrinsic interneuronal properties or represent a network phenomenon through, where the increased IED probability represents a consequence of disynaptic disinhibition.

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Fluctuations in DC potential and extracellular potassium concentrations precede seizures \textit{in vitro}

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The mechanisms of epileptic seizures are not well understood. In previous studies, we have shown that seizures are preceded by a loss of stability and resilience of brain tissue, which can be detected by changes in the early warning signals of critical slowdown. In this study, we focused on pathophysiological processes that could be responsible for the loss of neural network stability.

Seizures were induced in transverse hippocampal slices, which were perfused with low-calcium ACSF (0.1 mM). Spontaneous electrophysiological activity and DC potentials were recorded using glass microelectrodes positioned in the CA1 region. Extracellular potassium concentration was measured using potassium-selective electrodes.

The seizures were preceded by a tonic negative shift of the DC potential with superimposed slow phasic DC fluctuations lasting 0.5-3 s ($n = 12$) that could evolve into large-amplitude pre-ictal bursts. Analysis of current source density ($n = 4$) revealed, that fluctuations of the DC potential could arise due to depolarization in the pyramidal neurons. The unit activity revealed that slow fluctuations were accompanied by an increased probability of firing action potentials of pyramidal neurons (4.0 ± 0.7; $n = 42$) and interneurons (3.7 ± 0.9; $n = 22$). However, the firing probability analysis showed that interneuronal firing preceded pyramidal neurons firing by 150 ms. The slow waves were accompanied by an increase in extracellular potassium concentration (0.12 ± 0.02 mM; $n = 3$).

\textit{In vitro} seizures are preceded by phase fluctuations, which are characterized by a transient increase in neuronal activity and an increase in extracellular potassium. We hypothesize that the slow DC fluctuations reflect periods of brain tissue instability that are initiated by intense interneuronal activity. The results suggest that a similar mechanism may be shared by pre-ictal bursts and seizure onset. Optogenetic techniques should clarify the causal role of interneurons in these epileptiform phenomena and transition to seizure.

Pathological high-frequency oscillations mark the area of endogenous epileptogenicity in focal cortical dysplasia type II model

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High-frequency oscillations (HFOs) represent a potential electrographic marker of endogenous epileptogenicity. There is an ongoing debate whether the neocortical epileptic networks can generate HFOs of high frequencies. This stems from the absence of realistic models of neocortical epilepsy. In this study, we explored the pathological epileptiform network phenomena and HFOs in a highly realistic mouse model of neocortical epilepsy due to focal cortical dysplasia (FCD) type II.

FCD-related epilepsy in mice was generated by \textit{in utero} electroporation of mutant mTOR plasmid (p.Leu2427Pro) coexpressing GFP in E14.5 embryos. Adult mice were chronically recorded for at least 4 consecutive weeks ($N = 7$). Artifact-free periods of EEG data were selected, then the interictal discharges (IEDs) were detected automatically and screened for superimposed HFOs.

FCD lesion generated HFOs from the gamma, ripple, and fast ripple frequency bands. HFO rate was the highest in the peri-lesion 0.7±0.62; 95% CI[0.079, 1.3] (events/min) and lesional area 0.46±0.84; CI[0.13, 1.8] and lowest in the right frontal electrode 0.048±0.097; CI[0.014, 0.21] (events/min). The amplitude of HFOs in the lesion area was significantly higher than the amplitude of HFOs in the right frontal electrode (Friedman test, $P<0.001$). The results also demonstrated that fast ripples can propagate and contribute to their presence outside the lesion. There was no significant difference in IED rate across the electrodes.

In this study, we provide the first experimental evidence that FCD type II generates pathological HFOs. Properties of fast ripples mark the FCD lesion. The results support clinical observations that fast ripples should be considered during the presurgical evaluation in neocortical epilepsy. FCD type II model represents a unique opportunity to gain insights into the cellular mechanisms of how the epileptic brain generates pathological HFOs.
**BIDS Manager-Pipeline: a framework for multi-subject analysis in electrophysiology**

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**Purpose:** Processing large cohorts of data is very important to increase statistical power in neuroscience and neuroimaging. Brain Imaging Data Structure (BIDS) has been developed, in part, to overcome this problem. Structuring data in BIDS thus allows combining many subjects in a same analysis, in either single-center or multicenter studies. Our goal was thus to develop tools for collecting, transferring, organising and process automated analyses on data from different centers in the BIDS format.

**Methods:** BIDS Manager-Pipeline (BMP) builds upon BIDS Manager (Roehri et al. NeuroInformatics 2021;19:639-647), a software recently developed in our lab to collect, organise, and manage multimodal multicentre datasets. BMP coordinates the use of several modules originating from different software environments and executable programs and can thus be considered as a bridge between BIDS datasets and software solutions. Through a graphical user interface, users can filter the subjects of interest in the dataset by different criteria. BMP first controls whether the selected values and then run the process on all selected data. The results of analyses are stored using specifications for BIDS derivatives. In addition, BMP creates a table gathering the different metrics resulting from the analyses across subjects, for later statistical analyses.

**Results:** As a use case of the Medical Informatics Platform of the Human Brain Project, we converted iEEG and MRI data of the F-Tract project (f-tract.eu) in BIDS. Then, we performed automatic detection of epileptic spikes and oscillations on 40s-baseline sections in 50 subjects, using a software include in BMP. The results were stored in the derivatives section following BIDS format and the statistical table was generated.

**Conclusion:** BMP allows organizing and analysing data from large cohorts, either in basic neuroscience or in clinical research. This framework can take advantage of tools developed by the neuroscience community, centralizing and facilitating their use.

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**Fishing for antiseizure drugs in the North Sea, the discovery of halimide and plinabulin**

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**Purpose:** PharmaSea screened over 2000 marine extracts, using zebrafish embryos and larvae, to identify compounds with the potential to treat epilepsy. Among antiseizure hits was SK0107, one of the more polar fractions from the crude extract of *Aspergillus insuetus* IBT 28443, isolated from a seawater trap set in the North Sea. Bioactivity-guided purification led to the discovery of two new antiseizure compounds, the 2,5-diketopiperazine halimide and its analogue plinabulin. These are known microtubule destabilizing agents and plinabulin is a clinical drug candidate for the prevention of chemotherapy-induced neutropenia and treatment of non-small cell lung cancer. We here report their antiseizure and anti-epileptiform activity in the larval zebrafish pentylenetetrazole (PTZ) and ethyl ketopentenoate (EKP) seizure models, and investigated whether microtubule depolymerization could explain antiseizure action by antiseizure analysis of functional analogues colchicine and indibulin.

**Method:** Behavioral and electrophysiological antiseizure analysis in the zebrafish PTZ and EKP seizure models was performed using automated video recording and non-invasive local field potential brain recordings, as previously reported (WO2019043012 (PCT/EP2018/073147), Copmans D., et al.), after treatment of 2 or 18 hours via water immersion.

**Results:** Halimide significantly lowered PTZ-induced seizure behavior (p≤0.0001) and epileptiform brain activity (p≤0.01) at 200 µg/mL. Plinabulin ameliorated PTZ-induced seizure behavior at 1.25, 2.5, 5, and 10 µM (p≤0.0001) and epileptiform brain activity (p≤0.0001) at 10 µM. Plinabulin also significantly reduced EKP-induced seizure behavior at 1.25, 2.5, 5, and 10 µM (p≤0.0001) and epileptiform brain activity at 10 µM (p≤0.0001). Colchicine and indibulin were inactive against EKP-induced seizure behavior.

**Conclusion:** Halimide and plinabulin were identified as novel antiseizure compounds, demonstrating the potential of 2,5-diketopiperazines in general, and plinabulin in particular, for antiseizure drug discovery and development. Although the antiseizure mode-of-action is yet unclear, inactivity of functional analogues suggests that it is unrelated to microtubule depolymerization.
Timing matters for seizure-independent localization of the epileptogenic zone

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Purpose: Recently, multi-feature approaches have achieved better results in identifying the epileptogenic zone (EZ) than single features such as rates of epileptic spikes or high-frequency oscillations (HFOs). There are, however, important fluctuations in epileptic activity over time, and it is unknown how these changes affect the performance of localization algorithms. We hypothesize that pre-selection of patient-specific time segments will improve localization performance.

Method: We analyzed 60.5±15.8 hours/patient of stereo-EEG (SEEG) recordings from 34 drug-resistant focal epilepsy patients (16 good or Engel 1 post-surgical outcome). For each patient, we selected ten 5-min long interictal segments: random, random wake, random non-rapid eye movement (NREM) sleep, random N2, random N3, random REM, 1st 5 minutes of N2, maximum spike rate, minimum spike rate, minimum entropy. For EZ localization, we used a multi-feature model combining spike rates, HFO rates, relative entropy, coherence, and phase synchrony. The EZ was defined as resected seizure-onset zone contacts. The model was trained on Engel 1 patients. Segments were evaluated separately. Patients were tested by a leave-one-patient-out cross-validation. The performance of the model was evaluated by the area under the receiver operating characteristic curve (AUC). Differences across segments were tested by the Hanley-McNeal test with a multiple comparisons adjusted significance level of 0.05.

Results: Across all segments, the model achieved an average AUC of 0.86±0.03. Fluctuations were, however, marked between the individual segments (0.77-0.92). The best performance was achieved in the segment with a maximum spike rate, the worst with a minimum spike rate (p<0.001). AUC scores across segments correlated with spike rates (r=0.72; p=0.002).

Conclusion: Timing of the selection of segments for interictal EZ localization matters. While our multi-feature algorithm showed stable results, its performance was best when using the maximum spiking rate segment. In turn, periods with minimum spiking activity should be avoided for EZ localization.

Clinical Neurophysiology

3 Sensitivity of automated seizure detection tool in long term EEG monitoring

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Purpose: Automated seizure detection is increasingly utilized in clinical practice, for fast and accurate detection of epileptic seizures. The objective of this study was to assess the clinical yield of using automated seizure detection when evaluating long-term electroencephalography (EEG) recordings primarily in the Epilepsy Monitoring Unit (EMU).

Methods: We have retrospectively evaluated 100 consecutive EEG recordings (9 ambulatory sleep recordings, 91 EMU recordings). The recordings had a duration between 14 and 240 minutes (mean: 178 minutes), with a total of 17852 minutes. The recordings were analyzed using BESA Epilepsy 2.0 software. We compared the automated seizure detections of the software, with the visual findings from trained EEG experts.

Results: In the 100 recordings we found 276 epileptic seizures (116 focal, 160 generalized seizures). The algorithm identified 126 (45.7%) epileptic seizures in total. The vast majority of the missed 54.3% are generalized seizures (myoclonic seizures, tonic/atonic seizures and absences) and 38.8% of the focal seizures. The seizure detection software detected 294 episodes, which were false positive. The software did not detect any additional seizures in any patients, nor any seizure types that was not known.

Conclusions: The automatic seizure detection tool provided by BESA is not a time consuming process (it takes approximately <5 minutes in total), and can be helpful as an additional tool, but not on its own (un-supervised).
36 Electroclinical features and long-term therapeutic response in patients with typical absence seizures

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Purpose: We sought to characterize the electro-clinical features of typical absence seizures, and to elucidate whether EEG or semiology features can predict long-term therapeutic outcome.

Methods: We analysed video-EEG recordings from 213 typical absence seizures from 61 patients with idiopathic generalized epilepsy. We extracted semiology features, additional to the hallmark manifestations (motor/behavioural arrest and impairment of consciousness), their location, timing and frequency. We evaluated the duration and frequency of the spike-wave discharges and the presence of polyspikes. We used a supervised machine-learning approach to search for classifier features for long-term therapeutic outcome among 45 patients in the follow up group.

Results: Besides the hallmark manifestations, additional semiology features were identified in 87% (95%CI: 77.2-94.7) of the patients. The most common additional features were automatisms and eye blinking, in 67% (95% CI: 55.2-78.7) and 55.7% (95%CI: 43.2-68.1) of patients respectively. Automatisms were associated with longer seizure-duration (p< 0.0001) and oral automatisms occurred earlier compared to limb automatisms (4.03 vs. 6.19 seconds; p=0.005). The mean duration of the ictal spike-wave discharges was 9.06 seconds (SD: ±5.6), and the median frequency was 3 Hz. Polyspikes occurred in 46 seizures, 19 patients. Median follow-up was 5 years, and 73% (95%CI: 58-85.4) of the patients were seizure-free at end of follow up. None of the semiology features, alone or in combination were predictors of therapeutic outcome. The only significant classifier was the presence of polyspikes, predicting a not seizure-free outcome with an accuracy of 73% (95%CI: 70-77%), Positive Predictive Value of 92% (95%CI: 84-98%).

Conclusions: Semiology features in addition to behavioural arrest and non-responsiveness are common in typical absence seizures, but they do not predict long-term prognosis. Presence of polyspikes has a high positive predictive value for unfavourable therapeutic outcome, and their presence should be included when reporting EEGs in patients with typical absence seizures.

46 Automatic seizure detection framework

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Purpose: Development of an automatic seizure detection framework for electroencephalography (EEG) with high sensitivity and low false positive rate, which seamlessly integrates into the clinical workflow without requiring the presence of specific channels.

Method: The EEG frequency content is represented by continuous wavelet transform coefficients obtained using the complex Morlet wavelet in equidistant scales from 1 Hz to 30 Hz. From these coefficients, six features are extracted: minimum, maximum, root-mean-square, mean, standard deviation and skewness. These features are used to train a support vector machine classifier, which receives 30-second blocks as input. Each block is composed of five contiguous 6-second segments. This block configuration was chosen based on cross-validation training results (5-fold, leave-one-out).

For evaluation we used publicly available data from the Children’s Hospital Boston and Massachusetts Institute of Technology (CHB-MIT database, physionet.org): 23 cases from 22 subjects, ages 1.5 – 22, 21 channels, 256 Hz sampling frequency, totaling 952 hours of EEG with 171 marked seizures. Sensitivities and false positive rates/hour (FPR/h) were obtained for varying minimum-recruitment, namely, the amount of channels required to be classified as containing a seizure simultaneously. All methods are part of the CURRY 9 software (Compumedics Ltd., Abbotsford, Australia), including training/creation of custom classifiers based on this framework, as well as seamless addition of pre- and post processing steps (e.g. source reconstruction).

Results: Varying minimum-recruitment, the sensitivity-to-FPR trade-off can be balanced. For example, 19% minimum-recruitment yields 81% sensitivity and 0.7 FPR/h, having all seizures captured in 69% of the cases. In contrast, 42% minimum-recruitment yields 91% sensitivity and 3.2 FPR/h, having all seizures captured in 78% of the cases.

Conclusion: The framework reached top performance range in available commercial solutions (Baumgartner et al. Epilepsia 2018;59:14-22, Goenak et al. Seizure 2018;55:70-75) whilst offering flexibility and seamless integration into the clinical workflow within the CURRY software.
Subdural recordings more frequently result in surgical therapy than depth electrode recordings: a monocentric analysis in 443 consecutive patients undergoing intracranial preoperative evaluation

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Purpose: Intracranial recordings are used to define the epileptogenic region in complex cases with insufficient or inconsistent localizing information from non-invasive studies. The type of intracranial investigation greatly differs between centers without universal agreement as to the optimal diagnostic procedure. We here retrospectively analyzed outcomes of subdural and depth electrode recordings at the Freiburg epilepsy center to compare their diagnostic yield.

Method: 443 consecutive patients (347 lesional, 96 non-lesional) undergoing intracranial presurgical evaluation were analyzed using electronic charts and information from MR imaging and intracranial electrophysiology. 147 patients underwent purely subdural evaluation, 160 patients depth electrode recordings, and 136 a combined approach. Patients were analyzed as to whether (1) the epileptogenic region could be identified with certainty or approximately in lesional and non-lesional cases, (2) surgery was recommended.

Results: (1) In lesional epilepsy, in 63% of patients undergoing subdural recordings, 69% of patients with depth recordings, and 61% of patients with combined recordings were considered to have a clear definition of the seizure onset zone. In lesional epilepsy, 86% of patients undergoing subdural recordings, 64% of patients with depth recordings, and 83% of patients with combined recordings proceeded to surgery with a mean Engel I outcome of 60.8%. In non-lesional epilepsy, 63% of patients undergoing subdural recordings, 57% of patients with depth recordings, and 55% of patients with combined recordings proceeded to surgery with a mean Engel I outcome of 54.2%. (2) In both, temporal and frontal implantations of lesional patients, the rate of patients proceeding to surgery was higher following subdural recordings.

Conclusion: In both, non-lesional and lesional patients subdural and depth electrode recordings showed high rates of successful identification of the seizure onset zone. Significantly more patients with subdural recordings, however, proceeded to surgery, with similar rates of postoperative seizure control.

Is the flicker fusion appropriate to determine neurotoxic adverse events of antiseizure medication in epilepsy patients?

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Purpose: The critical flicker frequency (CFF) is defined as the frequency threshold when flickering light is perceived as continuous. Flicker frequency (FF) defines the frequency when previously continuous light appears as flickering. The CFF is a paradigm for neurotoxic adverse events of drugs in pharmacology and may be also influenced by disorders such as hepatic encephalopathy. Therefore, CFF and FF might be impaired in case of neurotoxic adverse events of antiseizure medication (ASM) and correlate with the amount of such side effects. This was investigated in this study in in-patients with normal cognition.

Method: Appropriate participants got a questionnaire and filled out the Adverse Event Profile form (AEP). We used a CFF device that produced red, green, blue or white flicker. In the patient group we repeated the measurement after one week (T2). CFF and FF were compared between patients and between patients and healthy controls. The correlation between alterations of CFF and FF with AEP results and the trough serum concentration of the ASMs was calculated.

Results: 33 people with epilepsy (PWE) and 20 healthy controls participated. At baseline (T1) four PWE reported neurotoxic adverse events by means of the AEP. At T2, two PWE remained. With the exception of the FF for green light CFF and FF were reduced in PWE compared to controls irrespective of their subjective reports. However, CFF and FF did not differ significantly between PWE with and without side effects. At T2 CFF and FF did not correlate with changes of AEP scores, serum concentrations or doses.

Conclusion: CFF and FF distinguish between PWE with ASM treatment and healthy controls. Within the group of PWE no further clinically helpful differentiation was possible.
Utility of prolonged outpatient EEG in the detection of interictal epileptiform discharges and its impact on clinical management

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Introduction: In patients with paroxysmal neurological events who are significant diagnostic challenges or in patients with refractory epilepsy, current guidelines recommend the use of longer-term monitoring. Outpatient ambulatory monitoring is a viable option in cases in which inpatient video-EEG monitoring is unavailable. Previous studies have shown that outpatient prolonged video-EEG monitoring yields a higher incidence of interictal epileptiform discharge (IED) detection compared to routine EEG and can aid in altering clinical diagnoses and management. We describe our centre’s experience with prolonged outpatient video-EEG monitoring in the past six years.

Methods: A retrospective study was performed in a 1000-bed academic university hospital in Singapore. 96 consecutive outpatient prolonged outpatient video-EEGs performed between 1 January 2016 to 31 May 2021 inclusive were analysed. No patients underwent drug tapering or sleep deprivation. EEGs were reviewed by 2 EEG-trained neurologists and relevant clinical details were collected.

Results: 96 EEGs were performed in 83 patients. The median (Q1:Q3) duration of prolonged EEG monitoring was 77.5 minutes (60:172.5). 62.5% of EEGs were performed on patients with a pre-existing diagnosis of epilepsy and 53.1% on those taking anti-seizure medication. 38 (39.6%) EEGs were performed for diagnostic clarity, 19 (19.8%) for localization of epileptogenic focus, and 39 (40.6%) to aid titration of anti-seizure medication. 35 (36.5%) prolonged EEGs performed captured interictal epileptiform discharges. 4 (11.4%) of these recordings were preceded by normal routine EEGs. On analysis of available video-EEG data, the median (Q1:Q3) time to first IED was 17 minutes (6:26). Changes in medication regimes were instituted following the results of 59.4% video-EEG recordings, with 11.5% of recordings leading to changes in diagnoses.

Conclusion: This single-centre study demonstrates the real-world utility of prolonged EEG monitoring.

The operational definition of epileptiform discharges significantly improves diagnostic accuracy of trainees in EEG reading

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Objective: To assess whether trainees can learn and implement the operational definition of interictal epileptiform discharges (IEDs) of the International Federation of Clinical Neurophysiology (IFCN), based on six morphological criteria, and whether its implementation improves their diagnostic performance.

Methods: Seven trainees evaluated a balanced dataset of 70 EEG samples containing sharp transients (35 from patients with epilepsy and 35 from patients with non-epileptic paroxysmal events). The gold standard was derived from video-EEG recordings of the habitual clinical episodes. The trainees individually reviewed the EEGs, blinded to all other data, in two successive training sessions, three months apart. The second session was preceded by a teaching module about the IFCN-criteria, and the trainees implemented them during the second reading session.

Results: By implementing the IFCN-criteria, trainees significantly improved their specificity (94.29% vs. 77.14%, p=0.01) and overall accuracy (81.43% vs. 64.29%, p=0.01) for identifying IEDs. Sensitivity also improved but it did not reach the level of statistical significance (77.14% vs. 60%, p=0.07).

Conclusions: Implementing the IFCN criteria significantly improves the diagnostic performance of trainees in identifying IEDs.
Validating EEG source imaging using intracranial electrical stimulation

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**Purpose:** To evaluate spatial accuracy of electrical source imaging (ESI) for known sources, using electrical stimulation potentials recorded on simultaneous stereo-EEG and 37-channel scalp EEG and to identify factors determining the localization error.

**Method:** In 11 patients undergoing simultaneous stereo-EEG and 37-channel scalp EEG recordings, sequential series of 99-110 biphasic pulses were applied on adjacent contacts of implanted stereo-EEG. ESI of averaged stimulation potentials was calculated utilizing a dipole source model on individual 4-compartment finite element method head models with various skull conductivities (0.0413-0.001 S/m). The localization error was calculated using Euclidean distance between the estimated dipoles and the center point between two stimulating contacts.

**Results:** 3,619 stimulation locations, respectively dipole localizations, were included. Mean localization errors ranged from 10.3 to 26 mm, depending on source depth and selected skull conductivity. The mean localization error increased with an increase of source depth (r=0.19, P<0.01) and decreased with an increase of skull conductivity (r=-0.26, P<0.01). Skull conductivity of 0.0206 S/m yielded lowest mean localization errors (12.8±5.6 mm) for all source depths. Using standard adult skull conductivity of 0.0042 S/m, mean localization error was 22.5±9.8, 14.4±5 and 15.4±8.6 mm for sources located in the mesial temporal structures, the lateral temporal cortex and the lateral frontal cortex respectively. In relation to stimulation locations, the majority of estimated dipoles moved inward-forward-downward to outward-forward-downward with an increase of source depth and a decrease of skull conductivity. An increase of source depth, the number of skull holes, and white matter volume, while decrease of skull conductivity independently led to higher localization error.

**Conclusion:** This evaluation of ESI accuracy using artificial patterns with high signal to noise ratio supports its application in presurgical epilepsy evaluation. Source depth and skull conductivity independently determine magnitude and offset direction of localization errors of estimated dipoles.

Posterior cingulate epilepsy: a systematic review

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**Purpose:** The cingulate gyrus is part of the limbic system and can be divided anatomically and functionally into the anterior, middle and posterior cingulate cortex. The middle region can be further partitioned into anterior and posterior parts according to their different connections. Cingulate epilepsies are rare and knowledge about posterior cingulate epilepsy (PCE) remains limited. PCE is often misleading because the seizure onset is located in an anatomically deep and semiologically silent area (Caruana F et al. Brain 2018;41(10):3035-3051). We aim at providing a description of posterior-middle cingulate epilepsy (pMCE) and PCE.

**Method:** A comprehensive search strategy was conducted in PubMed, Embase and Cochrane. Articles identifying patients with confirmed pMCE or PCE based on imaging, intracranial electroencephalography or surgery results were selected by two independent reviewers and included for analysis. Information concerning patient characteristics, ictal semiology, pre-surgical investigations, electrophysiological findings and surgery outcomes was retrieved.

**Results:** Thirty-four patients with pMCE and thirty-five patients with PCE were included in the analysis. The following numbers include patients with available data only. Many patients had daily seizures (32/69; 46%). The most frequent type of aura was sensory aura in both pMCE (18/34; 53%) and PCE (8/35; 23%). Motor components of seizures were predominantly tonic in pMCE (24/34; 71%) and automotor in PCE (11/35; 31%). Lateralizing signs were mostly contralateral to the epileptogenic zone. Impaired awareness was often reported in PCE (16/35; 46%) but less often in pMCE (5/34; 15%). Scalp electroencephalography localized more often to the anterior vertex in pMCE and to the temporal region in PCE. Surgical outcome was good (Engel Class I) in most patients (43/62; 69%).

**Conclusion:** These results provide an overview of the electroclinical features of pMCE and PCE. They highlight the importance of properly recognizing these types of epilepsy as they may be amenable to epilepsy surgery.
Relation of ictal/interictal connectivity patterns and 3D spike source analysis in subdural electroencephalographic recordings

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Purpose: To have a better understanding of localized and distant connectivity networks of interictal and ictal epileptiform discharges as a complementary analysis for presurgical evaluation.

Method: Focal epileptiform discharges (FEDs) are related to an abnormal region of the brain. Selected interictal and ictal discharges with a reasonable time constant patterns were identified for this study. We present a time and frequency domain cross-correlation analysis of in FEDs based on the number of connections (significance threshold p< 0.05) identified in the regions of interest in a case of lesional parieto-occipital super refractory epilepsy. A MATLAB environment was used, cross-correlation coefficients were calculated for each electrode pair using a time lag of ±500ms, where the maximum value was selected. Also, Curry 3D spike source analysis of FEDs was obtained by calculating the inverse problem in order to show significant onset activation areas in this case study. Functional connectivity maps were obtained from FEDs on subdural electroencephalographic data. The spatiotemporal modeling (moving dipole, rotating dipole, and CDR), was then superimposed on magnetic resonance imagery (MRI) in order to present the possible epileptogenic regions.

Results: Vascular lesion was located in the parietal occipital region in the right hemisphere. FEDs arising from this region were then evaluated in conjunction with functional connectivity analysis (time and frequency domains) in order to validate the propagation of the spikes. Most active regions, based on the number of connections, were located in the anterior part of the lesion, and there was a significant propagation in the occipital midline area and the ipsilateral temporal region.

Conclusion: This study shows that it is possible to relate FEDs in lesional areas, when placed in context with 3D spike source analysis, to abnormal “long distance networking” even in “normal” areas in the brain.

Multiple mechanisms shape the relationship between seizure pathways and seizure duration

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A seizure’s electrographic dynamics are characterised by its spatiotemporal evolution, also termed dynamical “pathway”, and the time it takes to complete that pathway, which results in the seizure’s duration. Both seizure pathways and durations have been shown to vary within the same patient. However, it is unclear whether seizures following the same pathway will have the same duration or if these features can vary independently. We compared within-subject variability in these seizure features using 1) epilepsy monitoring unit intracranial EEG (iEEG) recordings of 31 patients (mean 6.7 days, 16.5 seizures/subject), 2) NeuroVista chronic iEEG recordings of 10 patients (mean 521.2 days, 252.6 seizures/subject), and 3) chronic iEEG recordings of 3 dogs with focal-onset seizures (mean 324.4 days, 62.3 seizures/subject). While the strength of the relationship between seizure pathways and durations was highly subject-specific, in most subjects, changes in seizure pathways were only weakly to moderately associated with differences in seizure durations. The relationship between seizure pathways and durations was strengthened by seizures that were truncated versions of other seizures both in duration and in pathway (“truncated seizures”); but weakened by seizures that had a common pathway, but different durations (“elastic pathways”), or had similar durations, but followed different pathways (“duplicate durations”). Even in subjects with distinct populations of short and long seizures, seizure durations were not a reliable indicator of different seizure pathways. These findings suggest that seizure pathways and durations are modulated by different processes. Uncovering such modulators may reveal novel therapeutic targets for reducing seizure duration and severity.
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Dynamic properties of HFOs and spikes in the intra-operative electrocortigram in patients with focal cortical dysplasia

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**Purpose:** High frequency oscillations (HFOs) and spikes are known biomarkers for the epileptogenic focus. HFOs seem to have advantages overspikes, due to their specificity for the epileptogenic focus. The specific characteristics of HFOs and spikes for different pathologies in the intra-operative ECoG (ioECoG) has not been extensively investigated, while pathology specific knowledge can guide neurosurgeons during epilepsy surgery. We investigated the dynamics of HFOs and spikes for focal cortical dysplasia (FCD) patients with respect to the distribution, spreading and temporal properties.

**Methods:** People with epilepsy who underwent an ioECoG (4x5 AD-Tech grid) tailored resection, were selected from the UMCU RESPect database. Inclusion criteria were FCD confirmed by pathology and an Engel 1A outcome 1y post resection. Spikes, ripples (80-250Hz) and fast ripples (250-500Hz) in 1 minute ioECoG epochs pre-resection were automatically detected and visually checked. We compared the total number of events in- and outside resected area (RA, non-RA; independent t-test). We analyzed the timing of the HFOs and spikes by comparing the timing of HFOs in respect to the peak of the spike.

**Results:** We selected 22 patients (mean 19.2y) with FCD type 1A (n=2), 2A (n=6) and 2B (n=14). Spikes were found in 21 patients, ripples in 20 patients and fast ripples in 6 patients. The number of events found in electrodes covering the RA, edge and non-RA are for spikes: 1676, 265 and 746 (RA vs non-RA p<0.01); ripples: 977, 20 and 108 (p<0.01); fast ripples (FR): 214, 0 and 0 (p=0.01). Ripples on spikes occurred at the time of the peak, while fast ripples on spikes occurred on the rising flank of the spike.

**Conclusion:** FCD pathology is characterized by statistically difference in the number of ioECoG events, especially HFOs, between resected and not-resected tissue. This suggests that HFOs can be used to tailor epilepsy surgery in patients with FCD.

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A neuromorphic spiking neural network detects epileptic high frequency oscillations in the scalp EEG

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**Purpose:** Interictal High Frequency Oscillations (HFO) are measurable in scalp EEG. This development has aroused interest in investigating their potential as biomarkers of epileptogenesis, seizure propensity, disease severity, and treatment response. The demand for therapy monitoring in epilepsy has kindled interest in compact wearable electronic devices for long-term EEG recording. Spiking neural networks (SNN) have emerged as optimal architectures for embedding in compact low-power signal processing hardware.

**Method:** We analyzed 20 scalp EEG recordings from 11 pediatric focal lesional epilepsy patients. We designed a custom SNN to detect events of interest (EoI) in the 80-250 Hz ripple band and reject artifacts in the 500-900 Hz band.

**Results:** We identified the optimal SNN parameters to detect EoI and reject artifacts automatically. The occurrence of HFO thus detected was associated with active epilepsy with 80% accuracy. The HFO rate mirrored the decrease in seizure frequency in 8 patients (p = 0.0047). Overall, the HFO rate correlated with seizure frequency (rho = 0.90 CI [0.75 0.96], p < 0.0001, Spearman’s correlation).

**Conclusion:** The fully automated SNN detected clinically relevant HFO in the scalp EEG. This study is a further step towards non-invasive epilepsy monitoring with a low-power wearable device.
Deep learning and electrocorticography to tailor epilepsy surgery

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Purpose: Intra-operative electrocorticography (ioECoG) is used to delineate epileptogenic tissue. This delineation can be difficult due to the paucity of accurate epileptic ioECoG biomarkers. Computer-aided pattern recognition algorithms can be useful in the delineation process but need to be validated. This requires a large ioECoG dataset. Our aim is to construct a training and test set to train and validate a convolutional neural network (CNN) for binary classification of ioECoG channels as epileptic or non-epileptic.

Method: We retrospectively included patients who had an Engel 1A outcome from the RESPect database – a database with intracranial electroencephalography data from patients who underwent epilepsy surgery from 2008 on at University Medical Center Utrecht. Patients undergoing amygdala-hippocampectomy were excluded. The ioECoG channels were measured at 2048Hz and labelled as being inside or outside the resected area based on pre- and postresection photos. All resected channels were assumed epileptic, given that all patients had Engel 1A outcome. We split the patients into an 80% training and 20% test set after stratification by age and pathology. The CNN will be trained and validated to dichotomously classify single ioECoG channels on the training and test set, respectively.

Results: In total 113 patients (mean age: 18 [0-68] years) were included where 57 had frontal lobe epilepsy, 43 temporal lobe epilepsy, and 13 another anatomical location; 112 patients showed MRI abnormalities; 49 patients had tumour tissue, 39 cortical development malformation, 20 other pathology types, and 6 no abnormalities confirmed by pathology. Per patient, 1-6 pre-resection ioECoG recordings were made with 6-36 electrodes where at least 1 electrode covered the resection area.

Conclusion: This work is the first to build a large ioECoG dataset to train and validate a CNN. This dataset will be used to test whether a CNN can classify a single ioECoG channel as epileptic or non-epileptic.

Characteristics of absence seizures in relation to visuospatial attention

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Purpose: Absence seizures often affect attention. In particular, complaints related to unresponsiveness, visual allocation and maintenance of attention are consistent in patients with absences. Defining the relation between absence seizures characteristics and neurophysiological markers of visuospatial attention can help explaining clinical symptoms and may assist in prognostication and clinical advice.

Methods: We employed a within-subjects design to study the association of the EEG morphology and semiology of absences with visual attention. We included paediatric patients with generalized absence seizures at the Dutch tertiary epilepsy clinics Kempenhaeghe and Stichting Epilepsie Instellingen Nederland (SEIN). Patients performed a dedicated, 20-minutes-long computerized choice reaction time task, while EEG and eye-tracking outputs were synchronously recorded. We assessed reaction times (RTs) and features derived from eye movements. We used eye movements to subdivide RT into subcomponents, i.e. saccadic latency, saccadic duration and processing speed. Duration, frequency and morphology of ictal and interictal spike-wave discharges obtained from a 24h video-EEG investigation were correlated with RTs and eye movements.

Results: Our preliminary results include data from 10 patients with absence seizures, aged between 7 and 16 years. RT is significantly larger (p< 0.01) in patients who present paroxysms during the task performance. Furthermore, duration and frequency of the absences are associated with RT and RT subcomponents. Our pilot data further suggest that EEG characteristics of the absences (e.g. morphology of the spike-waves, amplitude or frequency) may also relate to markers of visuospatial attention.

Conclusion: We show that the degree of impairment of visual attention varies among patients with absences, depending on seizures characteristics, too. A fast assessment of visuospatial attention can be usefully employed in clinical practice to deliver advice tailored to the individual patient and for characterization and prognostication of patients with absence seizures.
Prevalence of epileptiform activity in early Alzheimer’s disease (AD)

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Introduction: Epileptic seizures are a known comorbidity of Alzheimer’s disease (AD). Epileptiform activity (even subclinical) as detected by 24-hour electro-encephalography (EEG) or magneto-encephalography has been reported in probable AD patients. Moreover, epileptiform activity might lead to disease progression in AD.

Purpose: To estimate the prevalence of epileptiform activity in preclinical AD and mild cognitive impairment (MCI) due to AD, as compared with healthy controls.

Methods: All subjects underwent a full neuropsychological examination, brain MRI and FDG-PET scans as well as lumbar puncture for analysis of core AD CSF biomarkers or PET amyloid. Subjects belonging to the AD continuum were diagnosed according to the NIA-AA research criteria. All exams were normal in the control group. All subjects underwent 24-hour EEG monitoring to detect epileptiform activity by means of automated spike detection. Due to its high sensitivity but low specificity, artefacts, sharp activity not clearly distinguishable from background rhythm and electropositive spikes on Average montage were removed by A.N. Remaining spikes were evaluated as being epileptic or not by our clinical epileptologist (L.S.), who was blinded to diagnosis.

Results: Preliminary data from the 24-hour EEG monitoring were reported. Epileptiform activity was detected in 3 out of 15 MCI patients, one out of 4 preclinical AD patients and in none of our healthy controls (n=3). The amount of spikes was 1, 2 and 10 per 24-hour EEG for MCI patients, 2 per 24 hour for our preclinical AD patient. Interestingly, MCI patients with epileptiform activity (median age 67 y/o [65;67]) were significantly younger than MCI patients without epileptiform activity (median age 72 y/o [68.75;76.75]) (p = 0.048).

Conclusion: Preliminary data of this ongoing study show that epileptiform activity is more prevalent in the AD continuum as compared to healthy controls. MCI patients with epileptiform activity were significantly younger than MCI patients without.

Can seizure cycles forecast outcomes of video-EEG: a prospective cohort study

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Purpose: A limitation of video-electroencephalography (vEEG) monitoring is the difficulty of capturing seizure activity during a non-specific monitoring time-frame. Recent work has confirmed self-reported seizure cycles can be used to generate forecasts of seizure likelihood (Karoly et al 2020). This novel forecasting framework could be implemented to identify an optimal vEEG monitoring time-frame. Here, we report preliminary results of a prospective study using personalised seizure forecasts to increase the yield of vEEG.

Method: Thirty-five adults (females = 28) referred for vEEG monitoring, with a diagnosis of active epilepsy (>1 seizure per month) were recruited. Participants recorded seizure events in a mobile seizure diary. Diary seizure times were utilized to detect an individual’s multiday cycle, and forecast dates of seizure risk. Follow up vEEG monitoring was scheduled according to the forecast of seizure risk (randomly allocated to high or low risk). Outcomes measures included: 1. Presence of epileptic events during monitoring. 2. Examination of EEG reports (normal/abnormal reports). 3. Assessment of EEG traces.

Results: At baseline EEG, 37% of participants presented with normal EEG, 49% with abnormal interictal activity but no confirmed seizure event and 14% with both abnormal interictal activity and confirmed seizure events. Here, we report preliminary findings from 4 participants whose 2nd EEG was based on their seizure risk forecast. There is promising early evidence of alignment between forecast and vEEG outcome. For instance, P1 presented with abnormal interictal activity and multiple seizures at baseline EEG, however, during subsequent vEEG (scheduled in low-risk), there were no confirmed seizure events. P2 presented with normal EEG at baseline and their subsequent vEEG (in high-risk) showed abnormal interictal activity.

Conclusion: Data from this ongoing study supports the need for optimised monitoring timeframes. Moreover, our preliminary data provides initial support for the efficacy of seizure forecasts for improving vEEG monitoring.
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Spectral factorization-based identification of seizure onset zone

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Purpose: Accurate localization of the epileptic seizure onset zones and their propagations, which usually depends on the information obtained from electroencephalography recordings, is crucial for successful epilepsy surgery. For this purpose, the analysis of high-frequency (>80 Hz) oscillations by non-parametric Granger Causality (NPGC) has been reported to be successful. The NPGC method, which uses heavy mathematical computations, relies on matrix spectral factorization (MSF). So far, the Wilson algorithm (WA) for MSF dominated in neuroscience applications, however, an alternative Janashia-Lagvilava algorithm (JLA) proved also to be effective and more accurate for noisy data. The aim of the study was to test capacities of JLA on real data obtained from ictal EEG recordings.

Methods: Two regions ( and ) of interest and a time epoch were isolated. In order to apply NPGC estimation for these regions, cpsd matrix was constructed in frequency domain by the multitapers method. The factorization , where is a transfer function and is a noise covariances matrix, was performed by JLA. The NPGC estimations and were computed for high frequency values by the standard formula using and . These estimations were used to confirm the visually suspected seizure onset region and its propagation.

Results: In place of the WA, the JLA was for the first time successfully used on specific real EEG data for localization of epileptic seizure onset and its propagation by NPGC. A thorough comparative analysis of these two algorithms should be the subject of the future work.

Conclusion: The recently developed JLA has the potential to substitute the WA which is widely used in computational neuroscience at present.

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The interictal automated responsiveness test (iART) analyzes transient cognitive impairment in an international manner

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Purpose: Intercital Automated Responsiveness Testing (iART) is an evolution of a standardized and validated test for measuring cognitive performance during epileptic seizures, Automated Responsiveness Testing in Epilepsy, developed in our laboratory. iART is designed to detect transient cognitive impairment (TCI) during brief interictal epileptiform discharges (IEDs).

Methods: iART tests orientation (time, person, place), language comprehension, word recall, word repetition, knowledge of body parts, left-right discrimination, apraxia, memory (e.g., time), and executive functions (e.g., persistence in enumerating numbers even though white noise is presented). Medical colleagues were contacted to translate the questions into their native language and to record the battery of questions using Zoom Video Communications software. Video files were saved in mp4 format.

Results: We recorded the question battery in Chinese, Arabic, Turkish, Greek, Russian, Lithuanian, Polish, Romanian, Czech, Croatian, German, Italian, French, Spanish, and Portuguese. A Python Script starts and stops the videos and can be controlled by a keyboard or by a TTL pulse. A scoring system was developed to quantify the extent of transient cognitive impairment by coding the patients’ responses: 0 for no response, 1 for a partially correct response, and 2 for a correct response. In this way, a maximum score of 80 can be achieved if all questions are answered correctly. Following the Mini-Mental State Examination or the Montreal Cognitive Assessment, a threshold of total score x 0.87 = 70 points was established to distinguish between normal or pure inattentional errors and IED-associated impairments. So far, the total score is recorded manually posthoc.

Conclusion: By internationalizing this test, there is the possibility of wider dissemination and better sensitivity and specificity for detecting IED-associated TCI, as the probability of correct answers is higher when patients are tested in their native language. It is possible to fully automate iART, e.g., through speech or video recognition.
Detection of focal epileptic seizures on EEG signals using the CSP algorithm

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Purpose: In the case of focal epilepsy, that its onset is limited to a specific cerebral region, the spatial information can be utilized for the seizure detection. A challenging issue is to use spatial filters in order to extract robust, representative features for seizure discrimination.

Methods: The CSP algorithm is an advanced signal processing method that enables the identification of spatial patterns representing underlying brain activity in multichannel signals [1]. The clinical dataset contained 8 drug resistant pediatric epileptic patients (3 females, 5 males) suffering from focal epilepsy recorded with long term video EEG whose age was 7.4±4.4 years. The dataset contained a total of 34 seizures. The CSP features of the EEG recordings that have been bandpass-filtered into multiple frequency bands corresponding to EEG rhythms. The mRMR feature selection algorithm was employed to rank each feature in terms of its importance and relevance to the investigated problem and various classification schemes were employed to categorize the multivariate timeseries data into normal and ictal states.

Results: Our proposed seizure detection system yields a best-achieved 10-fold cross-validation classification accuracy of 88.2% on EEG segments basis selecting 92 out of 96 features and utilizing the linear SVM classifier.

Conclusion: In this study, we propose a filterbank common spatial pattern algorithm for the detection of focal seizures. The proposed CSP algorithm identifies efficiently the ictal spatial patterns and is able to represent the local information in accordance with the pathology. It is characteristic that most of the patients of our study were suffering from right frontal epilepsy and this ictal local pattern was considered significant and represented efficiently by the CSP algorithm.


Epilepsy following a first seizure – quantum potential as a novel EEG biomarker

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Background: Predicting Epilepsy following a first seizure can be challenging. In clinical practice, the recurrence risk is estimated by the treating physician using the neurological examination, brain imaging, a thorough history for risk factors and routine scalp electroencephalogram (EEG) to detect abnormal epileptiform activity. The consequences can be significant regarding the initiation of anti-seizure medication (ASM) and e.g., driving restrictions. There is a great need for new biomarkers to better diagnose epilepsy following a first seizure. We developed a quantum potential mean and variability score (qpmvs), based on routine EEG recordings to identify accurately those patients prone to suffer from a recurrent seizure (epilepsy). The aim of our study is to test this method’s sensitivity and specificity to predict epilepsy following a first seizure.

Methods: We analyzed interictal EEG recordings of 70 patients admitted to the emergency department (ED) of a third referral center after a first seizure. Clinical data of the follow-up period of at least 18 months was available. EEG recordings of thirty healthy controls were also analyzed and included. For each EEG recording, we applied an automated algorithm to detect quantumpotentialmean and variability score (qpmvs) and detection of paroxysmal slow wave events (PSWES).

Results: Of patients presenting with a first seizure, 40% had a recurring seizure and were diagnosed with epilepsy. Sixty percent did not report additional seizures. Using a receiver operating characteristic (ROC) analysis we found that our approach can differentiate patients without a recurrence of seizures from those with a recurrence with high accuracy (AUC=0.924).

Conclusions: The quantumpotentialmean and variability score (qpmvs) and PSWES can predict epilepsy and help neurologists in evaluating a patient with a first seizure and might serve as novel EEG based biomarkers for predicting Epilepsy.
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**Bicentric retrospective study to evaluate the performance of ictal EEG source imaging to localize the epileptogenic focus**

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The objective of this study is to assess the performance of semi-automated ictal EEG Source Imaging (ESI) to localize the epileptogenic zone (EZ).

Sixty-eight patients from the Epilepsy Database Unit of Filadelfia Hospital (Denmark, n=51) and Saint-Luc Hospital (Belgium, n=17) were included in the study. At 1-year post-operational follow-up, 25/35(71%) case with temporal lobe epilepsy (TLE) and 15/33(45%) cases with extra-temporal lobe epilepsy (TLE) operation were seizure-free. EEG of Filadelfia cases was recorded with 25 channels, including 19 electrodes of 10-20 setup and electrodes F9/10, T9/10 and P9/10. In Saint-Luc the 10-20 setup was used. An expert electrophysiologist marked 148 electrographic seizure onsets (ETLE: 89/148(60%)) and indicated electrographic frequency-band of interest.

A 1s-length epoch was selected within first 3s after onset based on the EEG spectrogram and was mapped to source-space using ESI. Subsequently, spectral analysis was performed at each source and the one with the highest energy was identified as the seizure onset zone. Afterwards, it was compared to EZ derived from the post-operated MRI at sublobar-level. Based on the known surgical outcome after 1-year follow-up, the performance was quantified by calculating the sensitivity, specificity and accuracy to localize the EZ over all-seizures of all-patients. Furthermore, we assessed the performance at patient-level, where all seizures had to pinpoint to the resection in patients who were rendered seizure-free after surgery to be considered as a true-positive.

At seizure-level, the proposed method reached a sensitivity, specificity and accuracy of 73%,74%,74% for all-seizures, 79%,40%,66% for TLE-seizures and 68%,90%,79% for ETLE-seizures, respectively. At patient-level, however, the sensitivity, specificity and accuracy were 60%,68%,63% over all-patients, 76%,40%,66% for the TLE-patients and 33%,83%,61% for the ETLE-patients.

The results show the potential of ictal EEG source localization to localize the EZ. The results indicate that the method also work in the more complex ETLE cases.

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**High-density EEG-based network analysis reveals an anteroposterior network disruption in Idiopathic Generalized Epilepsy**

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**Purpose:** Idiopathic Generalized Epilepsy (IGE) involve both hemisphere at seizure onset with bilateral synchronous spike-wave discharges on EEG. However, brain networks can also be affected between seizures, as illustrated by cognitive deficits observed in some patients. Brain network analysis based on resting-state EEG analysis could bring additional value to improve the diagnostic approach.

**Method:** The project investigates the mechanisms underlying brain networks during resting state in patients with IGE, using prospective and retrospective data. Twenty adult patients (12 women, median age at EEG recording was 31.5 IQR [11], median epilepsy duration was 15.5 IQR [13]) were recruited from the University Hospital of Geneva. 20 healthy controls without any neurological disorders were recruited as a comparative group. All participants underwent a 256-channel EEG recording for 10-20 minutes in an awake, eyes closed condition and a T1-weighted MRI sequence (3T). Electric Source imaging was performed for 118 regions of interest from the Lausanne Atlas using an individual head model and distributed source model. We computed a connectivity matrix using the leakage-insensitive weighted phase lag index (wPLI) metric on 5s sliding time windows free of artefact with 50% overlap. We then calculated the average clustering coefficient and global efficiency to estimate the network segregation and integration.

**Result:** No significant differences in either segregation or integration were found between groups. However, we found a significantly different (p<0.01, FDR corrected) antero-posterior reorganization of local strength and clustering coefficient in several frequency bands with an increase in the anterior regions and a decrease in the posterior regions in patients vs controls.

**Conclusion:** Global network features are commonly shared in both healthy subjects and IGE but their spatial distribution profile differ. We revealed a network disruption involving frontal areas as key regions in IGE during resting state. This aspect could be possibly used as a diagnostic tool.
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**Interictal epileptiform EEG findings in elderly patients with epilepsy**

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**Purpose:** To examine the frequency of interictal epileptiform activity (IEA) and its relation to etiology and type of seizure.

**Method:** This retrospective study included 57 patients (37 male and 20 female), mean aged 67.2 years, with seizures onset at age 65 or over. Neurological examination, EEG (at least 4 interictal recordings), CT, Doppler sonography and cardiological evaluation were performed.

**Results:** The most common etiology was stroke (37% of patients). Alcohol abuse was present in 23% of cases, head injury in 14% and brain tumors or CNS infections in 10.5% of patients. The etiology remained unknown in 3 patients. Generalized tonic-colonic seizure was the most frequent type of seizure (46%). Partial seizures with or without secondary generalization were seen in 40% of patients. The rest of the patients (14%) experienced other types of seizures and 2 of them had non-convulsive status epilepticus (NCSE). Pathological EEG was found in 29 (50.1%) patients. Generalized discharges were detected in 7.0% of cases. Focal epileptiform activity or focal nonspecific activity was found in 12.3% of patients. In 19.3% of patients, EEG showed diffuse nonspecific activity. In two patients with NCSE (psychic changes in patients with previously diagnosed epilepsy), focal epileptiform activity in the EEG was crucial for treatment and cessation of NCSE. Pathological EEGs were significantly more frequent in patients with partial attacks, partial attacks with secondary generalization, atypical and myoclonic attacks in coma than in patients with generalized tonic-clonic seizures (p=0.10).

**Conclusion:** EEG was abnormal in half of patients. The frequency of IEA was quite low in comparison to nonspecific EEG changes. Analysis of EEG recordings failed to show the focal temporal slowing, possibly due to age of patients. The importance of EEG in elderly patients is especially significant in cases of NCSE where it plays a key role in treatment decisions.

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**Thalamic blood flow and simultaneously measured EEG frequency band power during hyperventilation in genetic generalized epilepsy**

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**Purpose:** Hyperventilation (HV) is a standard technique to trigger epileptiform discharges and absence seizures in genetic generalised epilepsy (GGE). We compare the effects of hyperventilation between individuals with GGE and healthy controls on thalamic cerebral blood flow (CBF) and electroencephalography (EEG) frequency band power.

**Method:** Thirteen patients (32.9±13.1 years, 9F/4M) with GGE and 18 healthy controls (34.8±11.3 years, 13F/5M) underwent EEG-MRI during three successive cued HV (24 breaths/min) and rest (free breathing) blocks. Pseudo-continuous arterial spin labelling images were acquired simultaneously and processed using Oxford_ASIL v4.0.16 (Chappell MA et al., IEEE Trans Signal Process2009;57(1):223-36). We sampled quantitative CBF maps within regions delineated via MAPER (Heckemann RA et al., NeuroImage 2010;51(1): 221-7). 32-channel EEG data were pre-processed using BrainVision Analyzer (v2.1, BrainProducts). We extracted the peak powers in the alpha (8-13Hz) and delta (1-4Hz) bands using FieldTrip (Oostenveld R et al., Comput Intell Neurosci 2011;156869) in MATLAB (R2020b, MathWorks).

**Results:** There was no difference in thalamic CBF between groups during rest, whereas delta power was higher in patients (0.077±0.037) than in controls (0.063±0.026; p=0.043). Hyperventilation was well-performed with no difference in respiratory rate between groups. CBF during HV differed between groups (repeated-measures ANOVA: p=0.036), with a decrease relative to baseline of ~12% in the controls and ~4% in patients. Alpha power was lower in patients (0.018±0.008) than in controls (0.022±0.008) during HV (p=0.02). Pooling rest and HV blocks, alpha (r=0.23, p=0.020) and delta (r=-0.36, p=0.001) power correlated with CBF in controls but not in patients.

**Conclusion:** Patients differed significantly from controls in delta power during rest, and in CBF and alpha power during HV. Patients also lacked the expected correlation between CBF and band power present in controls. The atypical effect of hyperventilation on thalamic CBF may contribute to the pathophysiology of GGE.
Effect of sleep on epileptic discharges in patients with Idiopathic Generalized Epilepsy

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Purpose: It is known that sleep and sleep deprivation affect the EEG findings, onset, frequency and semiology of the seizures. Generalized spike and wave discharges were found more common in drowsiness and sleep states, especially in childhood and juvenile absence epilepsy syndromes. In this study we aimed to show the effects of short sleep on the interictal and ictal discharges of the patients with genetic generalized epileptic seizures and to show the effects of treatment on the discharges during awake and sleep states.

Method: 37 patients (29 females and 8 males) with a diagnosis of genetic generalized epilepsy syndrome were included. All the patients were investigated with video-EEG recording during awake, sleep and post sleep states. Epileptic discharges were counted manually. Discharge numbers and their relation with triggers were analyzed to see the difference between different vigilance states.

Results: Number of ictal discharges is found to be increased after sleep. There was no difference in the control EEGs, which were taken under treatment.

Conclusion: Sleep is a trigger of epileptic discharges in ictal nature, but an effective antiepileptic treatment prevents this effect.

Comorbidities

Rasmussen syndrome secondary to neuroinfection by Epstein Barr virus. Description of the first case in Venezuela

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Purpose: Rasmussen disease is a progressive, inflammatory brain disorder that manifests as treatment-resistant focal neocortical motor seizures and culminates in severe deterioration with hemiparesis, cognitive retardation, and aphasia. Viral infections have been involved in the pathophysiology of this disease.

Method: 43-year-old female, with a history of multiple trauma with splenectomy 6 years ago, viral encephalitis due to Cytomegalovirus 4 years ago, toxoid vaccination 1 month before admission, who started a current disease one month before admission due to occipital headache a repetition radiating to the frontal region, mild to moderate intensity, intensifying, associating vomiting episodes, incoherent speech and confused thinking, later projectile vomiting accompanied by progressive deterioration of the state of consciousness until reaching stupor and left hemiparesis. On physical examination in poor general condition, stuporous, discrete fundus papilledema, neurological isochoric pupils with slow response to light, preserved cranial nerves, 3/5 left hemiparesis, generalized hyporeflexia, left Babinski. She presents greater neurological deterioration with focal seizures with repetitive motor manifestations in the left hemibody requiring mechanical ventilation.

Results: A new simple control brain tomography was performed, showing persistence of the unilateral hydrocephalus as well cerebral edema.

Conclusions: The present case represented a diagnostic challenge in view of the low frequency of cases of the disease, the lumbar puncture study never showed the presence of bacteria, only hyperprotein spinal cord and a predominantly lymphocytic count that never exceeded 500 cells and genetic demostration of Epstein Barr Virus. An electroencephalogram was performed where a unilateral hemispheric deceleration was evidenced. In view of the symptoms and the paraclinical findings, the criteria of the American Journal of Neurology on the disease were applied, finding a great concordance, management with immunoglobulin was established due to the neuroradiological and clinical findings, improving the neurological response of the patient.
Has the COVID-19 pandemic affected the seizure control status in patients with epilepsy?

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Purpose: To investigate the effects of the COVID-19 pandemic on the change in seizure control status in patients with epilepsy (PWE).

Methods: We included a consecutive sample of the adult PWE, who were registered in our database at Shiraz Epilepsy Center, Iran. In a phone call interview to all the selected patients on 10th to 30th July 2021, we obtained their current information if the patients agreed to participate. We compared the seizure control status of the patients in 2019 (pre-pandemic) with that during the COVID-19 pandemic.

Results: In total, 158 patients were included; 93 patients (58.9%) were seizure-free and 65 people (41.1%) were not seizure-free in 2019 (pre-pandemic era). Sixty-two patients (39.2%) had a stable status with respect to their seizure control. Many others had changes [less seizures (47 patients; 29.7%) or more seizures (50 patients; 31.6%)]. Thirty-two patients reported breakthrough seizures during the pandemic. Eighteen patients had an increase in their seizure frequency during the pandemic and 46 people had a decrease in their seizure frequency.

Conclusion: The COVID-19 pandemic has not acted as a major precipitating factor to affect the seizure control status in PWE as a whole. It is the natural history of treated epilepsy to fluctuate between periods of seizure freedom and relapse in many patients.

Sleep disorders in people living with drug-resistant epilepsy

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Purpose: Sleep disorders are one of the most frequent comorbidities of epilepsy. However, this condition is often underestimated or not evaluated during the epileptologic evaluation. Our study aims to describe sleep quality and daytime somnolence in drug-resistant epilepsy (DRE).

Method: We evaluated 643 patients admitted for VEEGM from January 2013 to December 2021 in our Epilepsy Monitoring Unit. All included patients fulfilled self-admistered tests of daytime somnolence and sleep quality, anxiety, depression and quality of life. We performed an univariate and multivariate analysis.

Results: A total of 493 drug-resistant patients were included with a median age of 38.83 years, 57.8% female. 60.2% had structural etiology, and 51.2% were temporal lobe epilepsy (TLE). Overall, 60.6% had poor sleep quality assessed by Pittsburgh Sleep Quality Index (PSQI). Assessed by Epworth Somnolence Scale (ESS) 61.3% had excessive daytime somnolence.

Beck Depression Inventory-II (BDI-II) showed that 49.6% had depressive symptoms and 29.2% according to Hospital Anxiety and Depression Scale-D (HAD-D). 44.4 and 49.5% presented pathological anxiety scores in State-Trait Anxiety Inventory STAI-T and STAI-S, respectively. 71.3% reported low quality of life (QOLIE-10).

In univariate analysis, depressive and anxiety symptoms, temporal lobe epilepsies, age, and female patients independently had significantly poorer sleep quality and higher daily somnolence (p<0.05). In the multivariate regression analysis of sleep quality (PSQI; R-squared: 0.401) we found significative influence of anxiety (HADS-A), depression (HADS-D) and poor quality of life (p<0.05).

Conclusion: Our data confirm the high incidence of sleep disorders in DRE patients and their impact on patients’ quality of life, highlighting the importance of considering the comorbidities between sleep disorders and epilepsy in the epileptological evaluation.
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Patient perspectives on anxiety and depression treatment and the collaborative care model of integrated care: a qualitative study

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Purpose: To evaluate epilepsy patient perspectives on treatment for anxiety and depression using qualitative methods and explore perspectives on a neurology clinic-based integrated care model (collaborative care).

Method: Participants in a study examining anxiety and depression among adults with epilepsy during usual neurology care completed semi-structured telephone interviews (NCT03879525). The interview guide explored experiences with anxiety and depression symptoms, treatment preferences, and care challenges. A description of neurology clinic-based collaborative care was followed by specific probes about this care model. Interviews were recorded, transcribed and cleaned. Reflexive thematic analysis was conducted using deductive and inductive approaches of Braun and Clarke. Two experts in qualitative analysis generated the codebook, coded all interviews and completed analysis using NVIVO software.

Results: The study sample (N=16) included 11 women (69%), 4 Blacks (25%), one Native American and one multiracial individual, with the remaining 63% being White/Non-Hispanic. Most participants indicated current significant impact of anxiety/depression on daily life, and many discussed a link between anxiety/depression and their epilepsy diagnosis, including fear related to SUDEP and other aspects of epilepsy. Most participants received treatment for anxiety and/or depression, commonly medications, therapy, or healthy living. Top challenges in seeking treatment were provider rapport/communication, transportation limitations, and individual hesitancy to seek treatment or add medication. Treatment facilitators included family, support groups, and neurologist efforts to facilitate treatment. Trust emerged as a key theme in provider interactions. In response to the neurology clinic-based collaborative care model description, the overall reaction was positive. Participants were generally comfortable with the role of a care manager, neurologist prescriber, and with psychiatry input via discussions with the care manager.

Conclusion: These adults with epilepsy responded positively to a potential neurology-clinic collaborative care model. Trust and provider rapport/communications were important drivers of mental health treatment experience.

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Exploring the experiences of self-determination of individuals with epilepsy and mild intellectual disabilities

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Purpose: Although self-determination is essential for subjective well-being and quality of life, there is a lack of knowledge about the experiences of self-determination of individuals with epilepsy and mild intellectual disabilities (ID). Therefore, we explored their experiences with respect to self-determination, operationalized by the three basic psychological needs of self-determination theory (i.e., autonomy, relatedness, and competence) and the role of the social environment in these experiences.

Method: Six adults with drug-resistant epilepsy and mild ID with adequate verbal communication skills were interviewed using a semi-structured interview guide. The interview guide was used to explore the experiences with respect to self-determination. The interviews were analyzed using Interpretative Phenomenological Analysis.

Results: The analysis showed that, although it contradicted with their own preferences, five out of the six participants have experienced pressure from family members or professionals to take protective measures related to the epilepsy, e.g., wearing a helmet. In addition, several participants – especially those who had their first seizure as teenager as opposed to those who had epilepsy from birth - experienced that epilepsy has a tremendous impact on their identity and self-esteem. That is, they had a hard time combining feelings of dependency and vulnerability due to epilepsy with feelings of equality and competence. Finally, several participants described to connect primarily with other people with epilepsy and ID in their care facility, whereas others expressed to form close relationships with people outside the care facility.

Conclusion: The experiences of the participants indicated that epilepsy affected their ability for decision making, especially regarding protective measures, influenced their identity and self-esteem and affected their feeling of relatedness to others. The results suggest that the influence of epilepsy on experiences of self-determination outweighs the impact of ID on these experiences. Further research with a more quantitative approach is recommended to validate the findings.
Incidence and types of bone fractures in people with epilepsy: a retrospective nationwide cohort study in North Macedonia

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Purpose: We aimed to evaluate the incidence and types of bone fractures among all prevalent epilepsy cases in North Macedonia between 2015 and 2018.

Method: Study participants were selected through a systematic search of the National Electronic Health Records platform. We identified all subjects with a diagnostic code of epilepsy (ICD-10 codes G40.0-9) and evidence of prescribed antiseizure medications (ASM). In this cohort, we searched for incident fractures (ICD-10 codes S00-99) during the study period. Patients were divided into three age groups: children and adolescents (0-19 years), young adults (20-49 years), and late midlife and elderly (older >50 years). Fractures were classified by location into seven groups: scull; jaw; vertebrae; shoulder and upper arm; lower arm; femur and upper leg; and lower leg. We calculated age-specific incidence rate ratios (IRR) for various fractures. Further, odds ratios (ORs) of fractures were estimated for the number of ASM.

Results: Out of 13825 prevalent epilepsy cases, 6383 (46.2%) were females and 7435 (53.8%) males. 1507 patients had a total of 1735 fractures; the age and sex-adjusted IRR was 1.48 (95% CI:1.27-1.72). Young adults had the highest IRR - 1.67 (95% CI:1.35-2.08), followed by middle-aged and elderly (older >50 years) - 1.53 (95% CI:1.17-2.01), while children and adolescents had the lowest IRR of 1.20 (95% CI:1.83-1.73). The most frequent were fractures of the jaw, the skull, and the vertebrae; IRR - 2.78 (95% CI:1.48-5.24), 1.95 (95% CI:1.35-2.83), and 1.83 (95% CI:1.20-2.79), respectively. Patients who received more than two ASM had significantly higher OR for any fracture 1.56 (95% CI:1.32-1.84), p=0.00, as well as for each fracture, except lower leg and upper arm.

Conclusion: This population-based study depicts a high incidence of fractures in people with epilepsy, particularly jaw and skull fractures. The use of more than two ASM was associated with a higher risk of fractures.

Headaches in patients with epilepsy – prevalence and risk factors

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Purpose: Headaches are considered a relevant comorbidity in epilepsy; however, available data are ambiguous. The aim of our study was to investigate the prevalence and risk factors for interictal headaches (IIH) and peri-ictal headaches (PIH) in patients with epilepsy (PWE) and to compare the prevalence of headaches among PWE and age- and gender-matched controls.

Method: Consecutive PWE seen in epilepsy clinic underwent a semi-structured interview regarding occurrence and characteristics of IIH and PIH. The following data were collected: demographics, age at onset of epilepsy, type of epilepsy, epilepsy treatment, frequency of seizures, IIH and PIH and their characteristics. Age- and gender-matched controls without epilepsy completed a questionnaire regarding headaches.

Results: A total of 300 (190, 63.3% females) PWE (median age 32 years ±12.6) were recruited. 185 (61.7%) patients had focal, 100 (33.3%) generalized, 4 (1.3%) combined generalized and focal and 11 (3.7%) unknown epilepsy. More than half of patients (160, 53.3%) were drug resistant, 138 (46.0%) were on polytherapy. Three quarters (211, 70.3%) of PWE reported IIH (migraine: 58, 27.5%, tension-type headache: 154, 73.3%) and in 138 (46.0%) subjects PIH occurred.

IIH were more frequent in females (69.2% vs 49.4%, p=0.002) and patients with drug-resistant epilepsy (58.3% vs 41.6%, p = 0.001), whereas PIH occurred more frequently in patients with drug-resistant epilepsy (63.8% vs 44.7%, p = 0.001) and on polytherapy (62.3% vs 32.3%, p<0.001). The prevalence of migraine was similar in PWE and controls (27.5% vs 25.4%, p = 0.68) whereas tension-type headaches were more common in PWE (73.3% vs 37.1, p <0.001).

Conclusion: Headache is a common comorbidity in patients with epilepsy. Intercital headaches are associated with female sex and drug resistance, perictal headaches with drug resistance and polytherapy. Tension-type headaches occur more frequently in PWE, the prevalence of migraine is similar among PWE and controls.
**Cannabidiol effects beyond seizures: preliminary data on emotional and behavioural symptoms and sleep quality**

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**Purpose:** Pharmaceutical formulation of Cannabidiol (CBD) (Epidiolex®; GW Research Ltd.) has been approved in recent years as add-on treatment for Lennox-Gastaut Syndrome and Dravet Syndrome. Cognitive impairment, emotional and behavioral symptoms, and sleep disturbances are among the most common and debilitating comorbidities in patients with drug-resistant epilepsy (DRE). CBD has been shown to have several mechanisms of action that result in neuroprotective, anti-inflammatory, anti-oxidant, and neurogenesis effects, thus leading to a possible cognitive effect on above-mentioned comorbidities. We report the results of a real word open label observational study aiming at investigating cognitive, behavioral effects and effects on sleeping of CBD as an add-on treatment.

**Method:** 15 Children and young adults patients affected by Lennox-Gastaut Syndrome due to different etiologies have been enrolled and evaluated before and after at least three months of treatment with Pharmaceutical formulation of Cannabidiol (CBD) (Epidiolex®; GW Research Ltd.). Standardized cognitive battery (Wechsler Intelligence Scales according to patients’ age, if possible), Adaptive Behavior Scale administered to the caregiver, self or proxy reports on emotional and behavioral symptoms (Child or Adult Behavior Checklist) and sleep quality questionnaire will be administered.

**Results:** Changes in cognitive, emotional-behavioral, and sleep quality before and after CBD introduction will be described by mean of descriptive statistics. Statistical correlation between seizure frequency and etiology will be provided.

**Conclusion:** Investigation into the effects of CBD on comorbidities in people with DRE is of high interest. Real word clinical studies are needs to evaluate side-effect profile from a cognitive and behavioral point of view in DRE patients receiving CBD.

**Drug Therapy**

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**NCC-1566, a novel Kir channel activator suppressed SUDEP and Status Epilepticus, and could be a potential drug for Dravet syndrome treatment**

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**Purpose:** Dravet syndrome (DS) is a severe epileptic encephalopathy with onset in infancy or early childhood. DS has a mortality rate of 15-20%. Sudden unexpected death (SUDEP) and death caused by status epilepticus (SE) account for 50% and 30% of all deaths in DS, respectively (Epilepsy&Behavior,2016;64:69). Loss of Kir4.1 channel function may be associated with SUDEP (Epilepsia,2021;6:143251). We previously demonstrated that NCC-1566, a first in class novel small molecule Kir channel activator, showed excellent in vivo anti-convulsive effects in various rodent models. In this study, we demonstrated effects of NCC-1566 on preclinical models of SUDEP and SE.

**Method:** As the SUDEP model, we used the audiogenic seizures model in DBA2N or DBA1 mice. In DBA2N mice SUDEP model, seizure response was scored, i.e. 0:no response, 1:wild running, 2:clonic seizure, 3:tonic seizure. In DBA1 mice SUDEP model, the rate of seizure-induced respiratory arrest (S-IRA) was evaluated. As the SE model, we used rat pilocarpine-induced SE model. The seizure intensity was scored by Racine's scale. The protective index (PI) was determined as the ratio of plasma concentrations in rotarod test (TC₅₀) to DBA2N mice SUDEP model (EC₅₀).

**Results:** In DBA2N mice SUDEP model, NCC-1566 suppressed clonic and tonic seizure with ED₅₀ = 5 mg/kg (N=8). In DBA1 mice SUDEP model, NCC-1566 suppressed S-IRA with ED₅₀ = 13 mg/kg (N=8-10). In SE model, NCC-1566 significantly reduced seizure intensity at 100 mg/kg (N=8). NCC-1566 did not show a significant decrease of latency to fall in the rotarod test at 300 mg/kg. The PI was more than 30.

**Conclusion:** These data suggested potential effect of NCC-1566 to suppress SUDEP and SE, which would improve mortality of DS. Moreover, NCC-1566 was expected to be wide safety margin because of the protective index. Therefore, NCC-1566 would be a highly attractive drug for the treatment of DS.
Levetiracetam pharmacokinetics and its relation to seizure frequency in pregnant women with epilepsy

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Purpose: To evaluate the levetiracetam clearance and its relation to seizure frequency in pregnant women with epilepsy

Method: Retrospective cohort study comprising 29 pregnancies in 27 women with epilepsy on levetiracetam (LEV) mono- or polytherapy. Concentrations of anti-seizure medications (ASMs), obtained during routine clinical practice, were used to calculate concentration/dose (C/D) ratio of LEV at least six months prior to conception (target concentration) and for each month during pregnancy. Seizure frequency and ASM dosages were obtained from patient records and ratio to target concentration (RTC) calculated. RTC-LEV course during pregnancy was analyzed using Linear Mixed Model analysis. The association of RTC-LEV with seizure increase (binary response) during pregnancy was analyzed using Generalized Estimating Equation analyses. Additionally, the discriminative value of RTC-LEV for seizure change was studied using Receiver Operating Characteristic curve analysis.

Results: C/D ratio’s decreased in 29 pregnancies throughout all months of pregnancy. In the seizure free group, seizure deterioration occurred in approximately 10% of patients, although the mean RTC-LEV was <0.5 from the second until the eight month. Whereas the association of RTC-LEV with seizure increase did not reach statistical significance in the total group (p=0.129), the association was statistically significant in the non-seizure free patients (p=0.022). RTC-LEV was inversely associated with seizure increase (B = -1.512, 95%CI: -2.803 – -0.221), indicating that a higher RTC-value is associated with less seizure increase. The area under the ROC curve was 0.688 [95%CI: 0.558 – 0.818], p=0.005. Moreover, RTC-lev ≤0.466 was the most optimal cut-off value concerning seizure change.

Conclusion: These new data stress the importance of therapeutic drug monitoring of LEV before and during pregnancy and contribute to a rational dosing paradigm. RTC-LEV is inversely associated with seizure increase, particularly in those patients that were not seizure free prior to pregnancy.

Definition of drug-resistant epilepsy: a reappraisal based on epilepsy types

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Purpose: To re-assess the definition of drug-resistant epilepsy based on the evidence from a large-scale, long-term study including both adults and children. We categorized the patients as idiopathic generalized epilepsies (IGEs), focal epilepsies, or structural-metabolic-genetic generalized epilepsies [symptomatic generalized epilepsies (SGEs)] and provided the definition of drug-resistance based on the epilepsy types of the patients.

Methods: This was a longitudinal study of a prospectively developed and maintained database. All patients with an electro-clinical diagnosis of IGE, focal epilepsy, or SGE, who received treatment from 2008 until 2021, were recruited at the outpatient epilepsy clinic at Shiraz University of Medical Sciences, Shiraz, Iran. All patients had to be followed at our center for at least 24 months. The receiver operating characteristic curve (ROC curve) was used for the statistical analysis.

Results: The included patients were: 523 with focal epilepsy, 218 with IGE, and 211 with SGE. For all epilepsy types, the ROC curves of the number of appropriately prescribed antiseizure medications (ASMs) were acceptable indicators to anticipate drug-resistance. The best cutoff point for focal epilepsies was at 4 ASMs (sensitivity: 0.56, specificity: 0.81); for IGE, at 3 ASMs (sensitivity: 0.51, specificity: 0.80); and for SGEs, at 4 ASMs (sensitivity: 0.78, specificity: 0.58).

Conclusion: The definition of drug-resistant epilepsy should be different in various epilepsy types. It is time for the scientific community to reappraise the definition of drug-resistant epilepsy in the light of the new evidence that has become available in the past 11 years since the previously published definition.
**65** Rational therapy with lamotrigine or levetiracetam: which one to select?

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**Purpose:** The aim of the current study was to investigate the seizure outcome and also factors associated with that in patients with epilepsy [i.e., idiopathic generalized epilepsies (IGEs), symptomatic generalized epilepsies (SGEs), and focal epilepsies], who received either lamotrigine (LTG) or levetiracetam (LEV).

**Methods:** This was a retrospective longitudinal study. All patients with a diagnosis of IGE, focal epilepsy, or SGE, who received either LTG or LEV, were recruited at the outpatient epilepsy clinic at Shiraz University of Medical Sciences, Shiraz, Iran. All patients had to be followed at our center for at least 14 months.

**Results:** Two hundred and thirty-six patients were studied (101 IGE, 98 focal epilepsy, and 37 SGE). At the first visit, LTG was prescribed for 159 patients; 40 people (25.2%) became seizure-free, and LEV was prescribed for 77 people; 23 persons (29.9%) became seizure-free (p = 0.438). Patients who were not taking any drug at the time of their first visit, or were receiving fewer drugs, and those who had received fewer drugs in their drug history were more likely to enjoy a seizure-free state at the follow-up. Among the patients, who received LTG at the first visit, taking any Na-channel blocking drug (e.g., carbamazepine) in the drug history was associated with a poor seizure outcome; this was not the case for LEV.

**Conclusion:** Implementation of appropriate personalized treatment plans in patients with epilepsy is of paramount significance. Rational selection of appropriate drug(s) is the mainstay of this process.

**67** Treatment outcomes by reason for adjunctive brivaracetam initiation in a real-life setting: post-hoc analysis of a European study

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**Purpose:** To evaluate effectiveness, quality of life (QoL), and tolerability of adjunctive brivaracetam (BRV) in patients aged ≥16 years with focal seizures by reason for BRV initiation in real-world practice.

**Method:** Patients received adjunctive BRV per clinical practice in a post-marketing, prospective, non-interventional European study (EP0077; NCT02687711). Post-hoc analyses were performed for the modified full analysis set (mFAS, subset of patients with BRV use per European SmPC) by reason for initiating BRV (lack of efficacy [LOE], any adverse events [AEs] including behavioral AEs [BAEs], or BAEs with current antiseizure medications [ASMs]).

**Results:** Of 310 patients in mFAS, 276 (89.0%), 74 (23.9%), and 49 (15.8%) initiated BRV due to LOE, any AEs, or BAEs with current ASMs, respectively (>1 reason could be selected). At baseline, the median number of focal seizures/28 days was 3.00, 1.33, and 1.17 in patients initiating BRV due to LOE, any AEs, or BAEs with current ASMs, respectively. At 12 months, BRV retention was 58.7%/58.1%/57.1% in patients initiating BRV due to LOE/any AEs/BAEs with current ASMs, respectively; and 50% responder rates were 64.6%/68.2%/76.9%. At 12 months, meaningful improvements in QOLIE-31-P total score were reported in 46.7%/47.1%/50.0% of patients initiating BRV due to LOE/any AEs/BAEs with current ASMs, respectively. At 12 months, most patients improved in Patient’s Global Impression of Change (PGIC) (54.2%/52.6%/53.8%) in patients initiating BRV due to LOE/any AEs/BAEs with current ASMs, respectively, and Clinical Global Impression of Change (CGIC) (61.0%/80.0%/72.7%). TEAEs were reported in 34.8%/33.8%/26.5% of patients initiating BRV due to LOE/any AEs/BAEs with current ASMs, respectively.

**Conclusion:** At 12 months, effectiveness (retention and 50% responder rates) and improvements in QoL (QOLIE-31-P total scores, PGIC, and CGIC) were observed, and BRV was generally well tolerated, independent of the reason for BRV initiation.

**Funding:** UCB Pharma-sponsored.
Big data analysis of ASM retention rates and expert ASM algorithm: a comparative study

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Purpose: Only 50% of patients with new-onset epilepsy achieve seizure freedom with their first antiseizure medication (ASM). A growing body of data illustrates the complexity of predicting ASM response, which is influenced by age, sex, and comorbidities. Randomized data with sufficient resolution for personalized medicine is unlikely to emerge. Two potential facilitators of ASM selection are big data using real-world retention rates or algorithms based on expert opinion. We asked how these methods compare in adult-onset focal epilepsy.

Method: Eight fictive cases were created and expert advice was collected from the algorithm Epipick. This was compared to real-world ASM retention rates calculated by cross-referencing data from comprehensive Swedish registers for 37,643 individuals, with identified co-morbidities. We evaluated the highest and lowest retention rates of the Epipick suggestions, and conversely, whether ranking based on retention rate reflected expert advice.

Results: The Epipick algorithm suggested six ASM alternatives for patients younger than 50 years and three ASM alternatives for older patients. In the real-world data, retention rates for the best expert opinion were high; 65-72% for young patients and 71-84% for older patients. The lowest retention rate for Epipick suggestions was 45-56% in younger cases, and 70-80% in older cases. The ASM with the best retention rate was generally recommended by the Epipick. We also investigated whether the drugs with the best retention rates were among those recommended by Epipick. If ASMs with more than 50 users were included, the highest-ranking ASM was among the Epipick suggestions in all cases.

Conclusion: We found a large overlap between expert advice and real-world retention rates. Notably, Epipick did suggest ASMs with more modest retention rates. Conversely, clearly inappropriate ASMs had high retention rates in some cases. In future clinical decision support systems, expert opinion and real-world retention rates could work synergistically.

Outcomes on efficacy and tolerability of cenobamate within an expanded access program

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Purpose: Early access program (EAP) provides earlier information about real-life use of antiseizure medication (ASM) after randomized control trials. This work analyzes EAP with cenobamate (CBM) in a series of patients with epilepsy in Spain.

Method: It is a multicenter, retrospective, observational study. Inclusion criteria for EAP were 1) older than 18 years; 2) focal seizures; 3) EAP authorization. At this interim analysis efficacy and safety outcomes were reported for those patients with a minimum follow-up of 3 months. The source of data was patient clinical records and time-points analyzed were baseline, 3 months and 6 months.

Response: A total of patients 97 patients were included, 61 patients reached 3 months and 37 patients 6 months of follow-up. At baseline, mean age was 39 (18-65), mean epilepsy duration was 28 years and mean number of seizures per month was 23 (1-250). Mean number of prior ASM (without including concomitant) was 9 (1-17) and mean number of concomitant ASM was 3. The mean daily dose was 166mg (25-300) and 194 mg (50-300) at 3 and 6 months respectively. No patient discontinued before 3 months and 2 patients discontinued at 6 months visit because of lack of efficacy. Regarding effectiveness at 3 and 6 months respectively, 80% and 64% were considered as ≥50% responder, 42% and 43% as ≥75% responder, 18% and 27% as ≥90% responder, 3.2% and 8% as seizure-free, 1.6% and 5% did worse. Cumulative adverse events (AE) at 3 and 6 months were reported by 72% and 81% patients respectively, mostly mild or moderate. The most frequent AE were somnolence, dizziness and balance disturbance.

Conclusion: Interim outcomes in a real-life very refractory population treated with CBM showed a high response. AE were reported in many patients but most of them were mild or moderate without leading to discontinuation.
104 Phase 2b Efficacy and safety of XEN1101, a novel potassium channel opener, in adults with focal onset seizures (X-TOLE)

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Purpose: This Phase 2b study was designed to assess the efficacy and safety of XEN1101 as adjunctive treatment in adults with focal onset seizures (FOS). XEN1101 is a novel, potent, selective KCNQ2/3 (Kv7.2/7.3) potassium channel positive allosteric opener being developed for FOS and major depressive disorder. Its pharmacokinetic properties support once daily oral dosing without titration.

Method: X-TOLE was a double-blind, placebo-controlled, dose-ranging study in adults. Subjects had ≥4 countable FOS per month, recorded with an eDiary, and stable treatment with 1-3 antiseizure medications (ASMs).

Results: A total of 325 subjects with a median baseline FOS frequency of 13.5/month were randomized and treated across four treatment groups in a 2:1:1:2 ratio (25mg: 20mg: 10mg: placebo). The trial met its primary and secondary endpoints with XEN1101 demonstrating a dose-dependent reduction from baseline in FOS frequency of 33.2% (p=0.035, n=46), 46.4% (p<0.001, n=51), and 52.8% (p<0.001, n=112) in the 10mg, 20mg, and 25mg groups, respectively, compared to placebo (18.2%, n=114). Responder rates of ≥50% reduction in FOS frequency were achieved in 28.3% (p=0.037), 43.1% (p<0.001) and 54.5% (p<0.001) in the 10mg, 20mg, and 25mg groups, respectively, compared to placebo (14.9%). Comparing CGI and PGI scores in the 25mg and placebo groups, approximately twice as many subjects reported at least much improvement with XEN1101: 46.4% vs 22.8% (p<0.001) and 42.9% vs 21.9% (p=0.001), respectively.

The incidence of TEAEs was 67.4%, 68.6%, and 85.1% in the 10mg, 20mg, and 25mg groups, respectively, compared to placebo (82.3%). The incidence of treatment-emergent SAEs was balanced across study arms. The overall dropout was 12.3%; 96.5% of study completers entered the open label extension.

Conclusion: At all doses, XEN1101 demonstrated a statistically significant reduction in FOS frequency compared to placebo and there was a corresponding dose-dependent improvement in responder rates. XEN1101 demonstrated a safety profile like other ASMs.

115 Non-seizure related outcomes with real-world use of cannabidiol in Lennox-Gastaut syndrome and Dravet syndrome: BECOME, a caregiver survey

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Purpose: We developed a cross-sectional caregiver survey, BECOME (global outcomes survey assessing changes in BEhavior, COgnition, and M ore with Epidiolex®), to characterise/quantify real-world seizure and non-seizure outcomes in patients with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS). This second abstract describes non-seizure behavioural and cognitive outcomes.

Method: US-based caregivers (N=498) of people with LGS (80%) or DS (20%) treated with plant-derived highly purified cannabidiol (CBD) medicine (Epidiolex® [GW Research Ltd], 100 mg/mL oral solution) for ≥3 months compared the past month to the period prior to CBD initiation. The survey included multiple choice and rank order questions using symmetrical 3-, 5-, and 7-point Likert scales (from worsening to improvement). Continuous variables were summarised as means, medians, and ranges, and categorical variables as frequency distributions and percentages. CBD-associated adverse events can include transaminase elevations, somnolence, decreased appetite, diarrhoea, pyrexia, vomiting, fatigue, rash, sleep disorders, and infections, but they were not assessed in this survey.

Results: A notable proportion of respondents reported improvements in ≥1 question for all domains: emotional functioning (82%), cognition and executive function (81%), language and communication in nonverbal (79%) and verbal patients (74%), activities of daily living (51%), sleep (51%), and physical functioning (46%). 6-26% of respondents reported worsening in ≥1 question of each domain. Most frequently reported improvements included: alertness (71% of respondents), learning new things (71%), being aware (70%), ability to engage with others (68%), paying attention (66%), happiness (66%), smiling (63%), saying sentences and phrases (58% and 60%), and calmness (56%).

Conclusion: Nearly all caregivers (93%) planned to continue CBD treatment, primarily because of reduced seizure burden but also because of improvements in non-seizure related outcomes.

Funding: Greenwich Biosciences
Seizure-related outcomes with real-world use of cannabidiol in Lennox-Gastaut syndrome and Dravet syndrome: BECOME, a caregiver survey

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**Purpose:** We developed a cross-sectional caregiver survey, BECOME (global outcomes survey assessing changes in BEhavior, COgnition, and More with Epidiolex®), to characterise/quantify real-world seizure and non-seizure outcomes in patients with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS). This first abstract describes seizure-related outcomes.

**Method:** US-based caregivers (N=498) of people with LGS (80%) or DS (20%) treated with plant-derived highly purified cannabidiol (CBD) medicine (Epidiolex® [GW Research Ltd], 100 mg/mL oral solution) for ≥3 months compared the past month to the period prior to CBD initiation. The survey included multiple choice and rank order questions using symmetrical 3-, 5- and 7-point Likert scales (from worsening to improvement). Continuous variables were summarised as means, medians and ranges, and categorical variables as frequency distributions and percentages. CBD-associated adverse events can include transaminase elevations, somnolence, decreased appetite, diarrhoea, pyrexia, vomiting, fatigue, rash, sleep disorders and infections, but they were not assessed in this survey.

**Results:** A notable proportion of respondents reported improvements in seizure frequency (84%), seizure severity (68%) and seizure free days per week (67%). A substantial proportion of caregivers reported improvements in convulsive seizures (72%), drop seizures (71%), non-convulsive/non-drop seizures (68%) and night-time seizures (62%). 6–22% of respondents reported worsening in ≥1 seizure outcome. Many respondents reported decreased number of emergency room visits (54%), hospitalisations (53%), seizure-related injuries (48%), and reductions in rescue medication use (57%). Seizure freedom (for at least the last month) was reported in 16% of patients.

**Conclusion:** Nearly all caregivers (93%) planned to continue CBD treatment, primarily because of reduced seizure burden but also because of improvements in non-seizure related outcomes, such as emotional function, alertness, cognition and communication.

**Funding:** Greenwich Biosciences

Non-seizure-related benefits of cannabidiol among patients with Dravet or Lennox-Gastaut syndromes: a qualitative study

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**Purpose:** This qualitative study aimed to increase understanding of the impact of cannabidiol (CBD) on non-seizure-related outcomes (e.g., behaviour, cognition, mood, and health-related quality of life [HRQoL]) among patients with Dravet syndrome (DS) or Lennox Gastaut syndrome (LGS) and their caregivers.

**Method:** Caregivers (N=21) were recruited of patients with DS (n=14) or LGS (n=7) in the UK, US, and Germany who have been treated with plant-derived highly purified CBD medicine (Epidiolex® [GW Research Ltd], 100 mg/mL oral solution) for ≥6 months. Participants were sent a background questionnaire. Interviews were conducted via telephone and explored the symptoms and impacts of DS and LGS, and non-seizure-related effects of CBD. Data were analysed using thematic analysis.

**Results:** Current symptoms included frequent seizures, cognitive impairment, communication, mobility and behavioural difficulties, sleep disruption, and reduced appetite. All patients required 24-hour supervision, and the majority (n=19) needed assistance with self-care. Caregivers reported that children’s symptoms impacted their overall HRQoL.

Most caregivers (n=19) reported beneficial HRQoL impacts of CBD, with improvements in awareness, mood, language, social skills, mobility, behaviour, appetite, school participation and information retention. Seizure frequency/severity reduction was also reported (n=16), resulting in caregivers having greater confidence to go out and socialise and having more time for themselves. A few caregivers (n=4) reported no effects, or only short-term beneficial effects. Some caregivers (n=10) reported adverse events of CBD, including loose stools, diarrhoea, somnolence, worsening behavioural difficulties, reduced appetite, and burning sensation in throat.

**Conclusion:** In addition to reduced seizure frequency, CBD may have a range of non-seizure-related beneficial effects, which warrant further investigation. Quantitative studies with larger sample sizes are required.

**Funding:** GW Pharmaceuticals Ltd
Clinical practice evidence for perampanel in epilepsy patients with tumour aetiology

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Purpose: To assess the real-world effectiveness, safety and tolerability of perampanel (PER) when used in everyday clinical practice to treat patients with epilepsy with tumour aetiology.

Method: Patients with epilepsy with tumour aetiology were identified from a pooled analysis of 44 prospective, retrospective and cross-sectional clinical practice studies. Retention was assessed after 3, 6 and 12 months of PER treatment. Effectiveness assessments comprised responder rate (≥50% seizure frequency reduction), seizure freedom rate (no seizures since at least the prior visit), and proportions of patients with unchanged or worsening seizure frequency. Safety and tolerability were assessed by evaluating adverse events (AEs), psychiatric AEs, and AEs leading to discontinuation.

Results: A total of 127 patients with focal-onset and/or generalised-onset seizures with tumour aetiology were identified (mean age, 46.6 years; mean duration of epilepsy, 9.7 years). Seizure types at baseline were focal-onset only (97.6%), generalised-onset only (1.6%), and focal-onset and generalised-onset (0.8%). Mean (standard deviation) PER doses at baseline and last visit were 2.6 (1.4) and 5.8 (2.5) mg/day, respectively. At 3, 6 and 12 months, retention rates were 88.0%, 79.5% and 65.3%, respectively. Reasons for discontinuation included AEs (16.8%) and lack of efficacy (5.3%). Mean (95% confidence interval) time under PER treatment was 11.0 (10.2–12.0) months. At the last visit (last observation carried forward), responder and seizure freedom rates were 66.9% and 34.2%, respectively, and the percentages of patients with unchanged or worsening seizure frequency were 15.8% and 6.8%, respectively. AEs were reported for 36.2% of patients; the most frequently reported AEs were dizziness/vertigo (13.8%) and somnolence (9.5%). AEs led to discontinuation of 16.8% of patients over 12 months and 13.0% of patients experienced psychiatric AEs.

Conclusions: PER was effective and generally well tolerated when used to treat patients with epilepsy with tumour aetiology in clinical practice.

Supported by Eisai
148 Pediatric and adult patients outcomes of an expanded access use program of cannabidiol in Spain

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Purpose: Antiseizure medication (ASM) expanded access program (EAP) provides earlier information about real-life use after randomized control trials (RCT). This study analyzes EAP with cannabidiol (CBD) in a series of patients with Lennox-Gastaut Syndrome (LGS), Dravet Syndrome (DS) and other encephalopathies

Method: Multicenter, retrospective, observational study. Inclusion criteria were: 1) included in EAP with at least 6 months of follow-up. 2) Patients or legal representatives agreed to participate. The source of data was patient clinical records and analyzed time-points included baseline, 3 months, 6 months, 1 year. Dosage, concomitant ASM, effectiveness including total and disabling seizures as drop or convulsive seizures and safety were evaluated.

Results: A total of 102 patients were included (60 patients LGS, 12 patients DS and 30 patients other) being 41.6% ≥ 14 year-old. Baseline median number of total and most disabling seizures per month was 33 and 15 respectively. The median number of prior and concomitant ASM was 7 and 3 respectively. Most frequent baseline ASM were valproate and clobazam. The mean dosage of CBD at 3, 6 and 12 months was 11,51±7.31 mg/kg, 13,44±8.52 mg/kg and 14,49±8.21 mg/Kg. Retention rate at 3 months, 6 months and 12 months was 91.2%, 78.4% and 61.4% respectively. Effectiveness regarding total seizures/most disabling seizures at 3 months, 6 months and 12 months showed 37.1%/36%, 44.9%/47.9% and 38.9%/40% of ≥50% responder. Seizure freedom at the last visit was achieved by 8.8% of patients. At the end of follow-up 51% of patients reported an improvement in the severity of seizures. Along the follow-up 66.7% patients reported adverse events being somnolence (34.3%), diarrhea (10.8%) and lack of appetite the most frequent. Two patients reported significant AST/ALT increase.

Conclusion: Outcomes in a real-life children and adult patient population treated with CBD showed similar outcomes in efficacy and tolerability that RCT.

150 Sex differences in side effects of antiseizure medications in pediatric patients with epilepsy: a systematic review

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Purpose: Sex-related differences in pharmacokinetic and pharmacodynamic of drug treatments have been highlighted since the first months of intrauterine life and become evident after puberty. However, little is known about the differences in efficacy and safety of antiseizure medications (ASMs) between boys and girls with epilepsy. Aim of the study was to perform a systematic review searching for differences in the side effects of ASMs with respect to sex in pediatric patients with epilepsy.

Method: We carried out a literature search of the PubMed database and all results up to April 2020 were included. Titles, abstracts and full texts were screened by two independent reviewers. We included all studies evaluating the side effects of ASMs in patients with epilepsy younger than 18 years, with reference to the two sexes.

Results: A total of 5164 studies were identified. Sixty-eight studies were included because they analyzed sex differences, of which 63 analyzed only pediatric patients and 5 mixed populations. Eighteen studies identified sex as a possible influential variable in terms of occurrence of side effects. In particular, although for some findings there were conflicting results from different studies, an overall higher frequency of adverse drug reactions in girls with different ASMs, a higher retinal toxicity in boys taking vigabatrin, higher BMI, leptin levels, hyperammonemia risk and carnitine deficiency in girls on valproic acid, a higher weight loss, more frequent acute psychosis and renal stones occurrence in girls on topiramate were reported.

Conclusion: Few studies analyzed sex differences in evaluating side effects of ASMs in pediatric populations, with sparse results. The findings of our study point to the presence of some differences, highlighting the need for a systematic evaluation of sex as a determinant variable influencing the response to medications in clinical research.
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Perampanel for the treatment of patients with myoclonic seizures in clinical practice

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Purpose: To assess the effectiveness, safety and tolerability of perampanel (PER) when used to treat patients with myoclonic seizures in everyday clinical practice.

Method: Patients with myoclonic seizures who were treated with PER were identified from a pooled analysis of 44 prospective/retrospective/cross-sectional clinical practice studies. Retention was assessed after 3, 6 and 12 months. Effectiveness assessments comprised responder rate (≥50% seizure frequency reduction), seizure freedom rate (no seizures since at least the prior visit), and proportions of patients with unchanged or worsening seizure frequency. Adverse events (AEs), psychiatric AEs, and AEs leading to discontinuation were evaluated.

Results: Overall, 156 patients with myoclonic seizures were identified. Patients had a range of epileptic syndromes; most commonly (>10% of patients), juvenile myoclonic epilepsy (72.9%) and idiopathic generalised epilepsy (13.2%). Mean (standard deviation) PER dose was 2.6 (1.1) mg/day at baseline and 5.5 (2.1) mg/day at the last visit (last observation carried forward). Retention rates at 3, 6 and 12 months were 94.7%, 89.0% and 80.7%, respectively. Reasons for discontinuation included AEs (11.4%), lack of efficacy (4.4%), and both AEs and lack of efficacy (2.6%). Mean (95% confidence interval) time under PER treatment was 12.1 (11.4–12.7) months. At the last visit, responder and seizure freedom rates were 85.9% and 63.4%, respectively; and the proportions of patients with unchanged and worsening seizure frequency were 10.2% and 3.1%, respectively. AEs were reported for 46.8% of patients and psychiatric AEs were reported for 24.7% of patients. The most frequently reported AEs (>5% of patients) were dizziness/vertigo (19.2%), somnolence (18.6%) and fatigue (9.6%). At 12 months, 14.0% of patients had discontinued due to AEs.

Conclusion: PER was effective and generally well-tolerated when used to treat patients with myoclonic seizures in everyday clinical practice. Almost two-thirds of patients achieved seizure freedom at last visit.

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Perampanel as early add-on therapy for epilepsy patients with focal-onset and generalised-onset seizures treated in clinical practice

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Purpose: To assess the real-world effectiveness and safety/tolerability of perampanel (PER) when used as early add-on therapy in everyday clinical practice.

Method: Patients treated with PER for focal-onset and/or generalised-onset seizures were identified from a pooled analysis of 44 prospective/retrospective/cross-sectional clinical practice studies. Data were compared for patients treated with PER as early versus late add-on therapy (as defined by each study). Retention was assessed after 3, 6 and 12 months of PER treatment. Effectiveness assessments comprised responder rate (≥50% seizure frequency reduction), seizure freedom rate (no seizures since at least the prior visit), and proportions of patients with unchanged or worsening seizure frequency. Adverse events (AEs), psychiatric AEs, and AEs leading to discontinuation were evaluated.

Results: 2532 patients were treated with PER as early (n=632) or late (n=1900) add-on therapy; median number of concomitant antiepileptic drugs were 1 and 3 at baseline, respectively. Retention rates were significantly higher for patients treated with early versus late add-on therapy at all timepoints (Month 12: 77.1% vs. 61.8%; p<0.001). At last visit, seizure freedom rate was significantly higher in patients treated with early versus late add-on therapy (40.1% vs. 8.7%; p<0.001), as was responder rate (73.0% vs. 36.4%; p<0.001); and the proportion of patients with unchanged seizure frequency was significantly lower in the early versus late add-on group (10.2% vs. 31.8%; p<0.001), as was the proportion of patients with worsening seizure frequency (6.1% vs. 13.6%; p<0.001). Patients treated with early versus late add-on therapy had a significantly lower incidence of AEs (41.8% vs. 54.5%; p<0.001), psychiatric AEs (18.3% vs. 22.2%; p=0.046), and discontinuation rates due to AEs at 12 months (15.0% vs. 18.7%; p=0.045).

Conclusion: PER was significantly more effective and better tolerated when used as early versus late add-on therapy to treat patients in everyday clinical practice.

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European Dravet Syndrome Advanced Therapies Working Group: an innovative patient-driven approach to accelerate research

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**Purpose:** Dravet syndrome (DS) is a rare and severe developmental and epileptic encephalopathy characterised by frequent seizures resistant to conventional antiseizure medications, as well as cognitive, psychomotor, language and behavioural problems. Since DS is caused in more than 80% of patients by a pathogenic variant in the *SCN1A* gene, disease-modifying advanced therapy medicinal products (ATMPs) are arising as potential definitive treatments for these patients.

Cooperation between laboratories is often hampered by scientific competition. We present the European Dravet Syndrome Advanced Therapies (EDSAT) Working Group, a pioneering initiative that aims to remove barriers between institutions to advance preclinical and clinical science in ATMPs for DS.

**Method:** EDSAT was launched in 2020 by Dravet Syndrome Foundation Spain (FSD), a patient advocacy organization (PAO) strongly involved in research. The consortium, to be presented at the congress, brings together the leading European experts investigating innovative therapies for DS. Regular project planning discussions and scientific brainstorming take place virtually and often include guest advisors. Tools are also shared by group members. In 2022, the Group organises an open workshop for early career scientists, where participants discuss ATMP approaches and models, exchange protocols, and network with renowned investigators, clinicians, industry representatives and regulatory experts.

**Results:** The EDSAT initiative helps researchers identify and deal with bottlenecks, foster intra- and interdisciplinary collaboration and speed up project timelines. In this way, FSD assists investigators to overcome common difficulties encountered during the development of their research.

**Conclusion:** This is the first time that laboratories working on ATMPs for DS are brought together in a framework of networking, mutual learning and collaboration. Importantly, this is also the first time that such a consortium is led by a PAO.

The EDSAT workshop received funding from the European Union’s Horizon 2020 research and innovation programme under the EJP RD COFUND-EJP N° 825575.

Assessment of vitamin D status and its association with seizure frequency and antiepileptic drug therapy in persons with drug resistant epilepsy

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**Purpose:** This study investigated the status of serum vitamin D level in persons with drug resistant epilepsy (DRE) and its association with seizure frequency and antiepileptic drugs (AEDs) treatment.

**Method:** This prospective observational study included persons with DRE of either gender (age 18-60 years) on stable AEDs treatment for at least 3 months. After screening and obtaining informed consent, patients were subjected for estimation of serum vitamin D level and those with vitamin D level <30 ng/ml were enrolled for this study. Demographic, seizures related and AEDs treatment related data were collected and the average seizure frequency per month at enrolment was recorded.

**Results:** Out of 95 enrolled patients, 43.16% had serum vitamin D level <10 ng/ml (severe deficiency), 33.68% had between 10-19 ng/ml (deficiency) and 23.16% had between 20-29 ng/ml (insufficiency). Correlation analysis of serum vitamin D level with seizure frequency did not show any significant association in persons with DRE. However, patients having average seizure frequency >12/ month had significantly lower vitamin D level as compared to those having ≤12 seizures/month (p=0.044). The median serum vitamin D level was numerically lower in persons with DRE on >4 AEDs ([7.81 (3-16.5)] ng/ml) as compared to patients on 4, 3 or 2 AEDs treatment though it was not statistically significant ([11.25 (3.07-25.5)], [11.1 (3-28.7)], and [10.8 (7.23-28)] ng/ml, respectively. Patients on AEDs therapy for >10 years had significantly lower level of median serum vitamin D level as compared to those on AEDs therapy for ≤10 years of duration (p=0.047).

**Conclusion:** Severe deficiency of vitamin D was associated with higher seizure frequency in persons with DRE. Addition of more AED for better seizure control also led to reduction in serum vitamin D level. Hence, early detection of vitamin D status and prompt supplementation may be helpful for better management of epilepsy.
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**Relationship between the ketogenic diet and epileptic seizures - a retrospective study with outpatients at the Centro Universitário Saúde ABC, Santo André, Brazil**

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**Purpose:** About 30% of epilepsy cases are drug-resistant and seizures are not controlled even with the use of two or more anti-seizure drugs (ASD). The ketogenic diet (KD), a high-fat, low-carbohydrate, and adequate-protein diet, is an effective and well-established non-pharmacological treatment method for drug-resistant epilepsy. Here, it was evaluated aspects related to epileptic seizure severity and adverse effects in patients undergoing a ketogenic diet with different proportions of grams of fat to grams of carbohydrate plus protein.

**Methodology:** A retrospective study was carried out with data (from March 2019 to now) from 24 patients at the KD outpatient clinic of the Centro Universitário Saúde ABC, Santo André, Brazil. Patients selected for the study were diagnosed with drug-resistant epilepsy and had been on KD for at least 3 months.

**Results:** Of the 24 patients, 62.5% were children, 8.3% adolescents and 29% adults (female 45.8% and male 54.1%). Regarding the types of diet, 54.2% used the 1:1 ratio (modified Adkins), 16.7% consumed 2:1, 16.7%, 3:1 and 12.5% 4:1. Approximately half of the patients experienced adverse effects such as dyslipidemia (45.5%), constipation (27.3%), and calculus (9%). Family members reported that patients had a decrease in aggressive behavior (71% of cases) and improved interaction with peers (61%). In addition, 79.1% of the patients showed a decrease in the severity of epileptic seizures. Of these patients, 2 became seizure-free, 2 had a 90-99% reduction in the number of seizures, 9 had a 50-90% decrease, and 6 had reduced the number of seizures to <50%.

**Conclusion:** Data from the study demonstrate that the use of a ketogenic diet considerably reduced the severity of epileptic seizures in patients diagnosed with drug-resistant epilepsy. The relationship between epileptic seizures and the proportion of diet consumed should be evaluated in further studies.

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**Upconversion nanoparticle-mediated optogenetics as a potential therapy for epilepsy**

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**Purpose:** Optogenetics has revolutionized a new era of effective and targeted control over neural function. Currently, we are still facing challenges in localized and effective long-term Epilepsy therapy. Combining both optics and genetics allows neurons to be controlled over specific spatial and temporal activity, a critical advance that will allow us to achieve an understanding of neurological disorders. However, it is limited since visible light cannot penetrate deeper brain structures. Upconversion nanoparticles (UCNPs) will up-convert lower-energy photons into one high-energy photon by absorbing the penetrable near-infrared (NIR) light and emitting wavelength-specific visible light, which will result in the manipulation of overexcited neurons.

**Method:** We aim to target GABAergic neurons found within Hippocampal cells using neuronal tissue surgically extracted from epileptic patients. The extracted neurons are first genetically engineered to express the excitatory light-sensitive protein, Channelrhodopsin. Furthermore, the UCNPs, Ytterbium and Erbium ions, are delivered to adhere to the genetically modified neurons. When these neurons were illuminated with the NIR light probe of the correct wavelength, the UCNPs converted the NIR light to visible light. As a result, the opsins were transiently activated, which inhibited the excitatory hippocampal cells and consequently dampened seizure activity.

**Results:** In this study, we have successfully genetically modified GABAergic neurons to express Channelrhodopsin. We synthesized and characterized the UCNPs using various light sources. Finally, the biocompatibility of the UCNPs was assessed, as well as Channelrhodopsin’s efficiency in inhibiting excitatory hippocampal cells to dampen seizure activity. These promising results will allow us to move forward for in-vivo studies.

**Conclusion:** Optogenetics is highly cell-specific while providing temporal resolution to acutely suppress seizures without interfering with standard behavior. In this approach, we have proven its feasibility and significant potential in seizure cessation.
Quality and sleep disturbances in paediatric patients with focal epilepsy after initiation of Perampanel as add-on therapy: preliminary data

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Purpose: Sleep disorders occur frequently in patients with epilepsy and are generally underdiagnosed.

Objective: To evaluate the impact of adjuvant treatment with Perampanel (PER) primarily on sleep quality and sleep disorders and secondarily on attention and executive functions in a paediatric population with focal epilepsy.

Method: Prospective and open-label ongoing study.

Children aged 4-18 years with focal epilepsy in whom PER was added to improve seizure control. PER 2mg/day was started and increased by 1mg every two weeks until best seizure control without any severe adverse effect. Sleep and cognitive scales were administered before and after 3 months following PER dose stabilization. Questionnaires used to evaluate sleep quality or disorders: Sleep disturbance scale from children (SDSC; pathological-score>39), Paediatric daytime sleepiness scale (PDSS; pathological-score>9) and Paediatric sleep questionnaire (PSQ; pathological-score>7). Epitrack Junior test (significant impairment<28) was used to assess cognitive impact.

Results: Of the 5 patients included (9-16 years, 80% female), 4 completed the study. Three patients showed >50% seizure reduction. Baseline sleep disturbances were detected in three patients (SDSC Raw-score pat1:44, pat3:50, pat4:58). At 3-months after PER, two patients improved but not normalized (SDCS pat3:41, pat4:47) and another normalized (SDCS pat1:35). All the patients showed baseline daytime sleepiness (PDSS pat1:13, pat2:8, pat3:21, pat4:21) that normalized in two patients on follow-up (PDSS pat2:5, pat4:7). No sleep-related breathing disorders were observed in any case with the PSQ. A significant attention/executive deficit was observed in two patients (EpiTrack<28 in pat2 and pat3: significant impairment). At follow-up, the two patients showed no significant change.

Conclusion: PER as an add-on therapy was shown to be beneficial in seizure reduction in 75% patients. The study didn’t show negative profile in sleep disorders (even normalized in 25% of cases), daytime sleepiness (even normalized in 50% of cases), sleep related breathing and cognitive performance.

A mirroring clinical practice study of perampanel in adults and adolescents: assessment of the impact of perampanel on quality of life and sleep in patients with focal-onset seizures

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Purpose: Here, we present quality of life (QoL) and sleep outcomes from A Mirroring Clinical Practice Study in Italy (AMPA; NCT04257604), which evaluated the effectiveness and safety of adjunctive perampanel in adult and adolescent patients with focal-onset seizures (FOS, with/without focal to bilateral tonic-clonic seizures [FBTCS]).

Method: AMPA was a prospective, observational study conducted in patients with FOS. Patients with insufficiently controlled seizures while receiving 1–3 anti-seizure medications were prescribed adjunctive perampanel per the approved indication. QoL and sleepiness were assessed at baseline and end of treatment (EoT; up to 12 months) in adult patients (aged ≥18 years) using the 31-item QoL in Epilepsy (QOLIE-31) questionnaire and Epworth Sleepiness Scale (ESS), respectively. A high score on QOLIE-31 and ESS reflects good QoL and greater sleepiness, respectively.

Results: Overall, 234 patients received adjunctive perampanel; 208 (88.9%) patients were aged ≥18 years. Mean (standard deviation [SD]) total QOLIE-31 score, based on seven QOLIE-31 domains, remained comparable between baseline and EoT: 56.0 (16.1) (n=203) and 57.7 (18.3) (n=160), respectively (mean [SD] change from baseline: 1.2 [14.2], n=157). Scores at baseline and EoT remained similar across majority QOLIE-31 domains; seizure worry showed the greatest improvement at EoT vs baseline (mean [SD] change: 7.1 [25.0]). Domains of emotional well-being (mean [SD] change: -1.7 [20.5]) and overall QoL (mean [SD] change: -1.8 [19.8]) had slightly lower scores at EoT vs baseline; however, these differences were not deemed clinically significant. The mean (SD) ESS score at EoT was 6.2 (4.4; n=177), which was similar to the baseline score (mean [SD] ESS score, 6.3 [4.5]; n=202; mean [SD] change in total ESS score, 0 [4.7]; n=174).

Conclusion: Overall, these data suggest that adjunctive perampanel does not negatively affect QoL or sleep following up to 12 months of treatment in adult patients with FOS.

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Assessment of cognition (EpiTrack®) and depression (Beck Depression Inventory-II) following perampanel (monotherapy/rirst adjunctive) in patients with epilepsy enrolled in the ELEVATE Phase IV study

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Purpose: Here we present results for change from baseline in cognition (EpiTrack) and depression scores (using the Beck Depression Inventory-II [BDI-II]) from ELEVATE (NCT03288129), a Phase IV study of perampanel administered as monotherapy/first adjunctive therapy in patients aged ≥4 years with focal-onset seizures (FOS), with or without focal to bilateral tonic-clonic seizures (FBTCS), or generalised tonic-clonic seizures (GTCS).

Method: ELEVATE consisted of Screening, Titration (≤13 weeks), Maintenance (39 weeks) and Follow-up (4 weeks) Periods. During Titration, patients received perampanel at 2 mg/day, which was titrated to 4 mg/day or higher, based on response and tolerability (maximum 12 mg/day). Dose increases were ≥2 weeks apart for patients taking non-enzyme-inducing anti-seizure medications (EIASMs) and weekly for those taking EIASMs. Cognition (EpiTrack) and depression (BDI-II) were assessed at baseline, and 3 and 12 months.

Results: Overall, 54 patients (FOS, n=38; GTCS, n=11; FOS+GTCS, n=5) were included in the Safety Analysis Set; 32 (59.3%) completed the study. Mean (standard deviation [SD]) change from baseline in EpiTrack total score at 12 months was -0.4 (3.3) (FOS, -0.6 [3.3]; GTCS, +1.6 [1.7]; increase = improvement). Five patients with FOS had improved shifts and six had worsening shifts from their baseline EpiTrack® score at 12 months. No shifts for patients with GTCS were observed. Mean (SD) change from baseline in BDI-II total score at 12 months was -1.2 (7.9) (FOS, -1.8 [8.0]; GTCS, +2.8 [8.3]; increase = worsening). Five patients (FOS, n=4; FOS+GTCS, n=1) had improved shifts and two patients (FOS, n=1; GTCS, n=1) had worsening shifts from their baseline BDI-II mood score at 12 months.

Conclusion: Perampanel did not negatively affect cognition with some patients reporting improvement at 12 months relative to baseline. There was no clinically relevant worsening of depression and the majority of patients remained within the same mood category.

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Digitalization in clinical epilepsy practice: methodology of BRITOBA study supporting digital health tool for better patient – physician interactions and patient-reported outcomes collection

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Purpose: Telemedicine and digital health solutions open new opportunities in delivering tailored care to patients through informing clinical decision-making, supporting patient-physician interactions, reducing uncertainties in outcomes and improving treatment precision. BRITOBA (EP0103) is a post-marketing, observational, prospective study currently conducted in Germany, France, Spain, Italy and Canada according to the real-world usage of brivaracetam (BRV) which is indicated for adjunctive therapy of focal seizures in patients aged 4 years and older in the European Union, and in adult patients in Canada. The study outcomes are 12-month effectiveness and tolerability of BRV in early treatment line combinations, health-related quality of life, treatment satisfaction, and work productivity in adult patients.

Method: BRITOBA allows participating sites and patients to use Helpilepsy™ (part of the Neuroventis platform) a certified medical device composed of a mobile health assistant for patients and a web-based dashboard for healthcare professionals, enabling real-time epilepsy monitoring for improved efficiency of care. More reliable and granular data can support physicians in their decision-making, while patients can benefit from adjusted treatment decisions based on their shared data. It could also result in a decrease of costs associated with additional hospital visits and consultations.

Results: The primary variable of the study is seizure freedom for ≥6 consecutive months over a 12-month observation period. Self-reported seizure frequency is collected through Helpilepsy daily during the first week, weekly during the rest of the first month, and monthly until end of the study period, and will be summarized using descriptive statistics for a better understanding of BRV effectiveness. Patient-reported questionnaires will also be completed on a voluntary basis in the mobile application.

Conclusion: The study is a unique opportunity for patients with epilepsy and their physicians to explore the potential benefits of using a digital solution for real-time disease monitoring in their clinical routine. UCB Pharma-sponsored.
Seizure treatment with olfactory training: a preliminary trial

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Purpose: Epilepsy is characterized by recurrent seizures and seen worldwide. Despite miscellaneous anticonvulsant drugs, resistance to treatment is still high. This resistance brings forward the multidisciplinary approach and complementary treatments. In this study, we aimed to investigate the effect of olfactory training on epileptic seizures with anticonvulsant aromas among patients diagnosed with drug-resistant epilepsy.

Method: A total of 24 patients (14 pediatric and 10 adults) with drug-resistant epilepsy were recruited for the study. Participants were asked to inhale the standardized bottle filled with lavender aroma (Lavandula Angustifolia) twice a day (morning and evening) for half a minute (2 cm in front of nose; 10-15 seconds to each nostril and 10-15 seconds to both nostril) for three months. In the beginning and at the end of third month, the number of seizure, duration and character of seizure of participants, the quality of life (SF-36 and PedsQL 4.0) and olfactory function (Sniffin' Sticks Test and Pediatric Smell Wheel) were re-assessed.

Results: Statistical analysis showed that olfactory training decreased the epileptic seizure frequency in both pediatric and adult patients (for pediatric p=0.005, z=-2.80; for adult p=0.027, z=-2.21) and also decreased the epileptic seizure duration (only for pediatric p=0.02; z=-2.20). Moreover, olfactory training increased the quality of life (p=0.003; z=-2.94) and improved the olfaction in both pediatric and adult patients (p=0.017; z=-2.37; p=0.05; z=-1.95; respectively). On the other hand, none of patients indicated adverse reaction and no increase in seizure frequency or no alteration in seizure character were seen.

Conclusion: It has been shown that olfactory training is a successful complementary therapy without adverse reaction in patients with drug-resistant epilepsy. Large cohort studies and long follow-up periods are needed for providing of olfactory training as a therapy modality in patients with epilepsy.

Personalised therapeutic management of epileptic patients guided by pathway-driven breath metabolomics

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Purpose: Therapeutic management of epilepsy remains a challenge, since optimal systemic antiseizure medication (ASM) concentrations do not always correlate with improved clinical outcome and minimal side effects. We tested the feasibility of noninvasive real-time breath metabolomics as an extension of traditional therapeutic drug monitoring for patient stratification by simultaneously monitoring drug-related and drug-modulated metabolites.

Methods: This proof-of-principle observational study involved 93 breath measurements of 54 pediatric patients monitored over a period of 2.5 years, along with an adult’s cohort of 37 patients measured in two different hospitals. Exhaled breath metabolome of epileptic patients was measured in real time using secondary electrospray ionisation–high-resolution mass spectrometry (SESI–HRMS).

Results: We show that systemic ASM concentrations could be predicted by the breath test. Total and free valproic acid (VPA, an ASM) is predicted with concordance correlation coefficient (CCC) of 0.63 and 0.66, respectively. We also find (i) high between- and within-subject heterogeneity in VPA metabolism; (ii) several amino acid metabolic pathways are significantly enriched (p < 0.01) in patients suffering from side effects; (iii) tyrosine metabolism is significantly enriched (p < 0.001), with downregulated pathway compounds in non-responders.

Conclusions: These results show that real-time breath analysis of epileptic patients provides reliable estimations of systemic drug concentrations along with risk estimates for drug response and side effects.
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Decrease in daily defined dose of antiseizure medications in Phase 3 trial of adjunctive cenobamate for focal seizures

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Purpose: An ongoing phase 3 safety study (C021), evaluated adjunctive cenobamate, an antiseizure medication (ASM) approved in Europe for adults with inadequately controlled focal seizures. This post-hoc analysis evaluated changes in concomitant ASM drug load and incidence of adverse events.

Methods: Patient ASM drug load was quantified using World Health Organization defined daily dose (DDD) at baseline and during post-baseline periods up to 30 months. Patients were grouped into 3 categories based on baseline DDD (0-<1, 1-<3, ≥3). Changes in DDD over time and incidence of treatment emergent adverse events (TEAEs) were reported for DDD categories.

Results: As of the June 2020 data cutoff (median treatment duration=33.4 months), 1340 patients were included in the post hoc analysis. Overall, the mean (SD) DDD at baseline was 2.86 (1.63) units, with 137 (10%) patients with DDD 0-<1, 607 (45%) with DDD 1-<3, and 596 (44%) with DDD ≥3. At month 30, the overall mean DDD reduction from baseline was 0.61 (1.01) units; in patients with baseline DDD ≥3, the mean DDD reduction was 1.14 (1.28) units. Patients with lower DDD at baseline had a lower incidence of TEAEs (0-<1: 99/137, 72%; 1-<3: 506/607, 83%; ≥3: 542/596, 91%) and serious TEAEs (0-<1: 3/137, 2%; 1-<3: 49/607, 8%; ≥3: 75/596, 13%) within a year of starting cenobamate. This pattern was observed among patients who experienced a TEAE (0-<1: 107/158, 68%; 1-<3: 413/582, 71%; ≥3: 234/314, 75%) or serious TEAE (0-<1: 8/158, 5%; 1-<3: 72/582, 12%; ≥3: 46/314, 15%) after a year of starting cenobamate.

Conclusion: A reduction in concomitant ASMs DDD in patients with focal epilepsy initiating adjunctive cenobamate was observed, with more than 1 unit reduction in patients with DDD ≥3 at baseline. Patients with lower DDD at baseline had fewer TEAEs and serious TEAEs.

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Final results of a mirroring clinical practice study of perampanel in adults and adolescents: a real-life, observational study of adjunctive perampanel for focal-onset seizures

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Purpose: Here, we present final results from A Mirroring Clinical Practice Study in Italy (AMPA; NCT04257604), which evaluated the effectiveness and safety of adjunctive perampanel in adult and adolescent patients with focal-onset seizures (FOS, with/without focal to bilateral tonic-clonic seizures [FBTCS]).

Method: AMPA was a prospective, observational study conducted in patients aged ≥12 years with FOS. Patients with insufficiently controlled seizures while receiving 1–3 anti-seizure medications (ASMs) were prescribed adjunctive perampanel per the approved indication. Seizure diaries and treatment-emergent adverse events (TEAEs) were verified at study visits (baseline and after 3, 6 and 12 months of treatment). The primary endpoint was percentage change in seizure frequency per 28 days at Month 6 (secondary endpoint, Month 12); other secondary endpoints were 50% and 75% responder rates, seizure-freedom rates, retention rates and monitoring of TEAEs up to 12 months.

Results: Overall, 234 patients received adjunctive perampanel (Safety Analysis Set); 135 patients completed the study. Perampanel was added to a median of 2 (range, 0–5) concomitant ASMs. Mean (standard deviation) modal dose of adjunctive perampanel was 5.8 (2.5) mg/day. Median (95% confidence interval) reductions from baseline in seizure frequency at Months 6 and 12 were 55.4% (46.7%–66.7%) and 69.2% (58.8%–76.1%), respectively, for FOS (with/without FBTCS) and 100.0% (93.3%–100.0%) and 100.0% (84.9%–100.0%), respectively, for FBTCS. At Month 12, the 50% and 75% responder rates were 63.5% and 44.5%, respectively, for FOS (with/without FBTCS), and 81.3% and 68.8%, respectively, for FBTCS. Seizure-freedom and retention rates at 12 months were 18.8% and 57.3%, respectively. Overall, 132 (56.4%) patients experienced TEAEs. The most common treatment-related TEAE was dizziness/vertigo (19.7%).

Conclusion: Final results from the AMPA Study suggest that adjunctive perampanel is effective and safe in adult and adolescent patients with FOS treated in a real-world clinical setting.

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**Effect of low dose (4 mg/day) perampanel on efficacy and safety outcomes from a mirroring clinical practice study of adjunctive perampanel in adults and adolescents with focal-onset seizures**

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**Purpose:** According to a pooled post hoc analysis of four Phase 3 studies, adjunctive perampanel 4 mg/day is efficacious in patients with focal-onset seizures (FOS), with/without focal to bilateral tonic-clonic seizures (FBTCS). Here, we report a post hoc analysis of the efficacy and safety of adjunctive perampanel 4 mg/day in adults and adolescents from A Mirroring Clinical Practice Study in Italy (AMPA; NCT04257604).

**Method:** AMPA was a prospective, observational study conducted in patients aged ≥12 years with FOS. Patients with insufficiently controlled seizures while receiving 1–3 anti-seizure medications were prescribed adjunctive perampanel per the approved indication. Seizure diaries and treatment-emergent adverse events (TEAEs) were verified at study visits (baseline and after 3/6/12 months of treatment). The primary endpoint was change from baseline in seizure frequency per 28 days at Month 6 (secondary endpoint, Month 12); other secondary endpoints were 50% and 75% responder rates, seizure-freedom rates, retention rates and monitoring of TEAEs up to 12 months.

**Results:** Of the 234 patients who received adjunctive perampanel, 62 (26.5%) received modal perampanel dose of 4 mg/day and were included in the Safety Analysis Set. Median reduction from baseline in all-seizure frequency was 55.4% (95% confidence interval [CI], 31.7%–90.3%) at Month 6 and 63.9% (95% CI, 31.7%–89.2%) at Month 12. The 50% and 75% responder rates were 57.1% and 46.9%, respectively, and seizure-freedom and retention rates were 26.0% and 46.8%, respectively, at Month 12. Overall, 50% of patients reported TEAEs with perampanel 4 mg/day. The most common TEAE was dizziness/vertigo (17.7% [n=11]).

**Conclusion:** This analysis further confirms that adjunctive perampanel at 4 mg/day is efficacious and safe in adult and adolescent patients with FOS, with/without FBTCS, treated in a real-world clinical setting.

**Funding:** Eisai s.r.l.

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**Design of Study 603: a multicentre, retrospective study in patients from Korea with focal-onset seizures who converted to perampanel monotherapy**

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**Purpose:** Here we present the design of Study 603, an ongoing multicentre, retrospective study assessing retention rates, efficacy and safety of perampanel as conversion from adjunctive therapy to monotherapy in Korean patients with focal-onset seizures (FOS), with/without focal to bilateral tonic-clonic seizures (FBTCS).

**Method:** Clinical data of eligible patients treated with perampanel will be obtained from electronic medical records at designated centres. Data will be categorised based on Baseline Period (start of adjunctive perampanel to withdrawal of other anti-seizure medications [ASMs]) and Analysis Period (start of conversion to perampanel monotherapy [i.e., 1 day after discontinuing other ASMs] to the end of perampanel conversion to monotherapy). Patients aged ≥12 years with FOS receiving perampanel as conversion from adjunctive to monotherapy since February 2016, with medical records for ≥3 months before perampanel was added and >4 weeks of the Baseline Period will be included. Primary endpoint: retention rates at 3/6/12 months after conversion to perampanel monotherapy. Secondary efficacy endpoints: retention rates at 3/6/12/18/24 months after adjunctive perampanel; change in standardised seizure frequency per 28 days and change in seizures between the Baseline Period and Analysis Period. Secondary safety endpoints: treatment-emergent adverse events (TEAEs), adverse drug reactions, serious TEAEs and TEAEs leading to perampanel discontinuation. Retention rates and safety endpoints will be assessed in all eligible patients who receive ≥1 dose of perampanel (Safety Analysis Set [SAS]). Efficacy endpoints will be assessed in all eligible patients from the SAS who receive perampanel monotherapy for >28 days (Full Analysis Set).

**Results:** The study was initiated in October 2020; 100 subjects will be enrolled at approximately 10 centres in South Korea.

**Conclusion:** Study 603 will provide real-world evidence regarding the retention, reduction in seizure frequency and safety profile of perampanel conversion to monotherapy in patients from Korea.

**Funding:** Eisai Korea Inc.
Personalised epilepsy therapy: gender-specific use of antiepileptic drugs in patients with pharmacoresistant

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Purpose: In the 21st century, the influence of antiepileptic drugs(AEDs) on patients’ quality of life has received great attention, and the topic of gender-specific use of antiepileptic drugs has gained considerable interest. The objective of this study was to examine the frequency of use of various AEDs in patients with pharmacoresistant epilepsy by gender.

Method: In 2020-2021, Polenov Neurosurgical Institute conducted a retrospective cohort study of AED treatment in 120 neurosurgical patients with pharmacoresistant epilepsy. We investigated gender-specific groups of patients and analyzed data using descriptive statistics.

Results: Men - group1; women - group2. The gender ratio – 1:1. The median age for both groups was 34 years. The disease lasted 19 years on average. In both groups, the use of old drugs prevailed in anamnesis (gr1 – 55 %, gr2 – 50 %), at the time of the survey new drugs predominated (gr1 – 47 %, gr2 – 57 %). Valproates dominated in group1: history – 19 %, at the time of the survey - 26 %, in group2: history of Valproate – 17 %, at the time of the survey: levetiracetam – 30 %, valproate – 10 %.

Conclusion: The use of valproates in women of reproductive age has significantly decreased, and drugs that are safer for the reproductive system are coming to the fore, this is in line with global trends and a personalized approach to the treatment of epilepsy.

Effectiveness of adjunctive perampanel in pediatric patients with drug-resistant epilepsy: an Italian multicenter observational cohort study

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Purpose: To assess efficacy and safety of adjunctive PER in pediatric patients with drug-resistant epilepsy, using retention and relapse-free survival rates as the outcome measures.

Method: Patients aged less than 18 years treated with PER from May 2015 to January 2022 were enrolled in this retrospective study. Kaplan-Meier survival analysis was made to assess the time to PER failure and the relapse-free survival in responders. The impact of epilepsy-related factors was evaluated using Cox Proportional Hazard Methods.

Results: The series comprised 133 patients (70 females) with a current median age of 15 years old (interquartile range [IQR]: 12-16 years), and 32 patients aged less than 12 years. The median age at seizure onset was 4 years (IQR: 1-7 years), and the median time of disease duration prior PER was 8 years (IQR 4-12). The epileptic syndromes were: generalized epilepsy (13.5%), focal epilepsy (65%), and epileptic encephalopathies (50%). The probability of remaining on PER was 65% at 12 months, 55% at 24 months, 41% at 36 months, and 41% at 48 months. PER was discontinued by 51 patients (38.34%) due to inefficacy (68.62%), side effects (13.72%), or both (17.64%). Twenty patients (15%) achieved seizure freedom, and 52 (39%) gained a significant (≥ 50%) seizure reduction. The presence of epileptic encephalopathy and cognitive impairment was significantly associated with PER failure (HR 2.51, 95% CI 1.44 – 4.37, p=0.001; HR 2.04; 95% CI 1.07-3.91, p=0.03, respectively).

The relapse-free survival in responders was 68.9% at 12 months, 46.3% at 24 months, and 30.2% at 36 months.

Conclusion: This study provides observational evidence for treatment persistence of PER in pediatric patients with drug-resistant epilepsy using time to treatment failure. The presence of epileptic encephalopathy and cognitive impairment should be kept in mind, particularly in younger ages, to optimize the use of PER in the clinical setting.
Eslicarbazepine in the treatment of status epilepticus

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Purpose: New anti-seizure medications (ASMs) are urgently needed for the treatment of SE. Due to the high mortality in treatment-refractory courses, substances with new mechanisms of action should be investigated in this urgent medical condition. In this study we evaluated efficacy and safety of eslicarbazepine acetate (ESL), a new sodium channel blocker, based on the data of a large epilepsy registry.

Methods: Data on the efficacy and safety of ESL in the treatment of refractory SE was gathered from the Mainz Epilepsy Registry. Logistic regression was applied to identify predictors of status interruption.

Results: 64 patients with refractory SE aged 61.4 +/- 11.0 years were treated with ESL. The median number of previously administered ASMs before the use of ESL was 3. On average, 2 days had elapsed since the onset of status epilepticus until administration of ESL. The initial dose of ESL was 800mg/d and then increased up to a maximum daily dose of 1600mg in case of non-response. In 29 out of 64 patients (45.3%), the SE could be interrupted within 48 hours of ESL therapy. Compared to other etiologies of SE, the best control of SE was achieved in patients with poststroke epilepsy (62%, i.e. in 15 out of 23 patients). Days of SE before initiation of therapy with ESL were an independent predictor of control of SE. Hyponatremia occurred in 5 patients (7.8%). Other side effects were not observed.

Discussion: Based on the data presented herein, ESL may be considered as effective and safe adjunct therapy in the treatment of refractory SE. The best response was found in patients with poststroke epilepsy. In addition, early initiation of therapy with ESL appears to result in better control of status epilepticus. Our observational study shows promising data for future randomized controlled trials in this indication.

Real-world healthcare costs related to long or short-half-life antiseizure medication use

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Purpose: Long half-life (LHL) antiseizure medications (ASMs) remain in systemic circulation longer compared with short half-life (SHL) ASMs. A LHL-ASM (> 20 hours) may be more protective of missed doses, at any adherence level, resulting in better efficacy and improved outcomes. Our objective was to compare healthcare costs in patients treated with LHL- versus SHL-ASMs.

Methods: This retrospective cohort study used the IBM MarketScan® Research database to identify patients >18 years old with epilepsy (≥2 medical claims ≥30 days apart), ≥2 fills for an SHL or LHL-ASM (first fill was index date) between 1/1/2016–12/31/2018, and 12 months’ continuous enrollment pre- and post-index. Patients who received any ASM in the pre-index period or both SHL plus LHL-ASM post-index were excluded. Adherence was assessed over the 12-month post-index period using the proportion of days covered (PDC). Medical claims were used to estimate healthcare costs, where epilepsy-related costs were defined as a claim that had a primary or secondary epilepsy diagnosis code. A generalized linear model with gamma distribution was performed for adjusted healthcare costs.

Results: A total of 7,144 patients were identified (4,866 SHL, 2,278 LHL). Compared to SHL, patients receiving LHL-ASMs were significantly younger (37.7 versus 43.4 years, p < 0.001) and less comorbid [Charlson comorbidity index: 0.6 versus 1.7, p < 0.001]. Adherence to therapy was similar between SHL and LHL-ASM (mean PDC 0.65 vs. 0.63). Patients receiving LHL-ASMs had lower mean all-cause per-patient-per-month (PPPM) costs ($1,365 vs. $4,282) and epilepsy-related ($273 vs. $610) (all p < 0.001). After adjusting for demographics and clinical characteristics, LHL-ASM users had lower PPPM mean all-cause costs ($2,028 vs. $3,942) and lower epilepsy-related costs ($293 vs. $553) (all p < 0.001).

Conclusion: Patients treated with LHL monotherapy had a lower economic burden compared with those treated with SHL, indicating that using ASMs with a longer half-life is associated with lower healthcare costs.
Clinical characteristics of patients achieving seizure freedom in a Phase 2 trial evaluating adjunctive cenobamate

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Purpose: Cenobamate is an antiseizure medication (ASM) approved in Europe as adjunctive therapy for adults with inadequately controlled focal seizures. This post-hoc analysis examined baseline clinical characteristics of patients who became seizure free with cenobamate treatment during the open label extension (OLE) of Study C017.

Methods: A double-blind, randomized, placebo-controlled, dose-response study evaluated cenobamate treatment in adults with focal seizures despite therapy with 1-3 concomitant ASMs through ≥1 year of follow up. Post-hoc analysis of patients who achieved seizure freedom (zero seizures for ≥1 year) examined duration of epilepsy, concomitant ASMs, number of previously failed ASMs, and seizure type reported in these patients.

Results: As of June 2020, 23.2% (65/280) of participants achieved seizure freedom for ≥1 year from the first day of the OLE study. Seizure free patients had a median duration of epilepsy of 24.2 years compared with a median duration of 24.4 years for patients who did not achieve seizure freedom. Analysis of concomitant ASM grouped by mechanism of action found that 25.5% of those taking concomitant GABA_A modulators and 23.5% of those taking GABA_A modulators with benzodiazepines or sodium channel blockers were seizure free for ≥1 year. Among patients who experienced secondarily generalized tonic-clonic seizures, focal onset unaware seizures, or focal onset aware seizures at baseline, 27.6%, 22.3%, and 17.5% achieved seizure freedom for ≥1 year, respectively.

Conclusions: Nearly a quarter of patients treated with cenobamate experienced total seizure freedom for at least 1 year in the long-term follow-up. This proportion was generally consistent across diverse types of patient characteristics at baseline.

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Sleep-wake cycle and daytime sleepiness in patients with epilepsy after initiating perampanel as adjunctive therapy

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Purpose: Antiseizure medications have been shown to impact positively or negatively sleep and/or daytime sleepiness, however, few studies have assessed the effect of perampanel on these aspects with objective measures. Therefore, this study aimed at evaluating sleep-wake cycle and daytime sleepiness in patients with epilepsy initiating perampanel as adjunctive therapy.

Method: This prospective and observational study included patients with epilepsy aged ≥ 18 who received as add-on perampanel. Sleep-wake cycle was assessed through actigraphy monitoring and daytime sleepiness with Multiple Sleep Latency Test (MSLT; 4x20 minute trials) at baseline (T0) and 6-month follow-up (T1) visit after initiating perampanel. The Whitney Rank test was used to evaluate the changes in seizure frequency, actigraphic sleep-wake measures and daytime sleepiness.

Results: Ten patients (mean age: 44.50 ± 22.71 years, 50.0% female) were included. The mean illness duration was 14.20±13.21 years and the mean monthly seizure frequency was 3.20±5.94 [1-20]). The majority of patients (n=6; 60%) started perampanel as a first add-on, while 20% (n=2) started as a second and the other 20% (n=2) as a third add-on. The final perampanel dose was 5.11±2.02 and seizure freedom was achieved by 90% of patients. There was a significant decrease in mean monthly seizure frequency (p=0.004) from baseline (3.20±5.94) to 6-month follow-up (0.50±1.58). No significant changes were found in sleep-wake parameters measured through actigraphy. At 6-month follow-up, an increase in the sleep latency mean was observed at MSLT trials (p=0.005; T0 13.15±4.11; T1 17.99±2.87).

Conclusion: This study suggests that adjunctive perampanel improves seizure control without impairing sleep-wake cycle; remarkably objective daytime sleepiness improved in patients with epilepsy. Considering our findings and previous evidence, perampanel may present a positive effect on sleep and daytime sleepiness.
Sleep architecture improvement after lacosamide monotherapy in patients with epilepsy

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**Purpose:** The relationship between sleep and epilepsy is bidirectional, and antiseizure medication may directly or indirectly impair or improve sleep. This study evaluated the effect of lacosamide as monotherapy on sleep architecture in adult patients with epilepsy.

**Method:** This prospective study enrolled 10 patients with epilepsy aged ≥18 starting lacosamide. Sleep was assessed through polysomnography (PSG) at baseline (T0) and 6-month follow-up visit (T1). At T1, patients were also evaluated with Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Quality of Life in Epilepsy Inventory (QoL 31), Beck Depression Inventory (BDI) and with the EPItrack. Changes in PSG from baseline to follow-up was assessed through Wilcoxon rank-sum test. Correlations between delta PSG change scores and questionnaires were tested with Spearman test.

**Results:** All 10 patients (mean age: 58.00±14.77 years, 60.0% female, mean monthly seizure frequency: 1.20±2.48) achieved seizure freedom at follow-up. Sleep efficiency significantly improved from baseline (76.88±7.81) to follow-up (85.81±6.37). A significant decrease was documented in sleep latency (T0 9.27±9.45; T1 5.13±4.44), wake after sleep onset (T0 100.15±34.88; T1 65.67±35.95), and percentage of stage 3 (T0 6.70±3.87; T1 3.84±1.93) and stage 3 of Non-REM sleep (T0 28.09±8.10; T1 21.95±8.69). REM duration increased from baseline (12.11±9.32) to follow-up (18.14±6.43) without reaching significance. Moreover, delta change of N3 positively correlated with EPItrack subtests of interference (rho=0.66), trail making test A (rho=0.76) and B (rho=0.72). Delta change of both N1 and REM latency was negatively correlated with ESS (rho=-0.66; rho=-0.67); and delta change of total sleep time negatively correlated with QoL (rho=-0.71).

**Conclusion:** This study suggests that lacosamide monotherapy may positively modify sleep architecture in patients with epilepsy, highlighting a correlation between sleep stability and executive function and QoL. These findings are possibly linked to seizure control achievement. Thus, lacosamide may be a suitable antiseizure medication especially in patients with poor sleep quality.

Adjunctive cenobamate in severe drug-resistant epilepsy: an Irish retrospective cohort study

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**Purpose:** In 2019, the United States Food and Drug Administration approved the use of cenobamate for focal drug-resistant epilepsy (DRE). Cenobamate inhibits voltage-gated sodium channels and is a positive GABA_A modulator. Here, we studied the effectiveness and tolerability of cenobamate in a cohort of ‘real-world’ patients with DRE who previously failed multiple anti-seizure medications (ASMs).

**Methods:** A retrospective study of consecutive patients treated with cenobamate for focal DRE attending a tertiary neurology centre. All patients received cenobamate through an early managed access program (MAP). Clinical data was obtained from our epilepsy-specific electronic patient record. We conducted clinical interviews with patients and relatives/caregivers to ascertain treatment response and side-effects. A fixed dosing regimen was applied. Up-titration to 200 mg daily was achieved over 12 weeks. Further dose adjustments were decided by the treating physician (maximum dose of 400mg daily).

**Results:** Thirty-one patients were included. Mean age was 38.5 years (range 18-63 years). Seventeen patients had focal seizures only, while four had combined focal and generalised seizures. Sixteen patients had a structural aetiology, four had genetic epilepsy, two had an infectious aetiology, two had immune-mediated epilepsy and the aetiology was unknown in seven patients. Before starting cenobamate, mean seizure frequency was 82 per month (range 8-240). All previously trialled multiple ASMs (median=12; range 4 -21). Fourteen patients had prior epilepsy surgery and 22 had vagus nerve stimulation. Mean duration of treatment was seven months (range 3-13 months). Two patients achieved seizure freedom (6.5%). Eleven patients (35.5%) had a 75-99% seizure reduction, while eight (25.8%) had a 50-75% seizure reduction. Two patients (6.5%) discontinued treatment due to side-effects and two developed phenytoin toxicity, highlighting this important pharmacokinetic interaction.

**Conclusion:** Cenobamate displayed favourable effectiveness and tolerability in this adult cohort with highly refractory focal epilepsy.

**Acknowledgements:** Cenobamate was accessed through Angelini Pharma’s MAP
**Efficacy of perampanel in patients with Unverricht-Lundborg disease (EPM1)**

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**Purpose:** To evaluate the efficacy and safety of perampanel (PER) administered as add-on therapy in patients with (ULD)

**Method:** We treated 3 males with genetically confirmed ULD (aged 25-29 years, epilepsy onset at 8-10 years) with disabling, pharmaco-resistant myoclonus. PER was introduced by 2 mg steps at 2–4 week intervals up to 10mg/day.

**Results:** Patient 1 (25yo), independent, ambulation with help, multiple myoclonus daily, PER was added to valproate (VPA), topiramate (TPM), levetiracetam (LEV), and increased to 10mg/day. Sustained reduction on myoclonus by 50% was observed during one year follow-up. Patient 2 (29yo), independent, ambulation without help, daily myoclonus leading to falls, PER was added to VPA, LEV, clonazepam (CLZ) and increased to 4mg/day. Sustained reduction on myoclonus by 75% was observed during six months follow-up. Patient 3 (28yo), wheel-chair bound, constant myoclonus, PER was added to VPA, TPM, LEV, CLZ, and increased to 8mg/day. Sustained reduction on myoclonus by 50% was observed during six months follow-up. The patient is able to walk with assistance. No psychological and behavioral side-effects were observed. Weight gain between 2-5 kg was reported by all patients.

**Conclusion:** This study provides evidence that for ULD patients, PER may show marked efficacy even in severe cases, particularly against myoclonus. PER should thus be tried in ULD patients whose seizures are not satisfactorily controlled. Its use may be limited because of side effects. Given the limited scientific evidence, broader prospective trials should be encouraged.

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**Safety of brand-to-generic lacosamide switch - a prospective observational study**

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**Purpose:** To determine the clinical outcomes of brand-to-generic lacosamide (LCM) switch in patients with epilepsy.

**Method:** This prospective observational study included all patients treated with LCM in the University Hospital in Kraków in October 2018. In October 2018 the price of the brand-name LCM in Poland increased by up to 17 times in comparison to the generic products. Assuming that the majority of the patients would be forced to switch to generic drugs due to financial issues we decided to follow them prospectively for 4 months to evaluate the safety of switching from brand-name to generic LCM. Data on seizure frequency and adverse events were collected from the patients’ seizure diaries.

**Results:** Overall 81 (45 males, aged 18-62 years) were included in the study. All patients suffered from focal epilepsy and were treated with LCM as add-on therapy. The most commonly used combination therapies included levetiracetam and valproate. The decision to switch or not to switch was made by patients alone and was based on financial reasons. Only two patients (2.5%) decided to continue on brand-name LCM, the vast majority switched to generic products. We did not find differences in terms of frequency of seizures and adverse events between patients continuing on brand-name LCM and those switching to generic antiseizure medication.

**Conclusion:** The switching from brand-name to generic LCM seems to be safe, however, larger prospective studies are required in order to confirm our findings.
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Retrospective chart review study of use of cannabidiol (CBD) independent of concomitant clobazam in patients with Lennox-Gastaut syndrome or Dravet syndrome: interim analysis

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Purpose: CBD (Epidyolex®; GW Pharma [International] B.V.) is approved in the EU and UK as adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), in conjunction with clobazam, in patients ≥2 years of age. An ongoing retrospective chart review (GWEP20052) aims to evaluate CBD use without clobazam in patients aged ≥2 years with LGS or DS enrolled in a European Expanded Access Programme. This interim analysis reports data collected through 15 November 2021.

Method: Data were collected from patient charts from 3 months before initiation of CBD without clobazam. Data collection was stopped at 12 months of treatment, or sooner if a patient discontinued CBD or started clobazam. Patient characteristics and safety were assessed for patients who received CBD without clobazam for ≥3 months. Retention was calculated using Kaplan-Meier methods.

Results: Data were available for 45 patients (36 LGS, 5 DS, 4 unknown) who received CBD without clobazam for ≤12 months, of whom 43 were treated for ≥3 months. Mean (SD) age: 15.7 (11.8) years; 49% male (n=41). Time-averaged CBD dose through 3 months: 10.7 mg/kg/day (n=37). Retention on CBD without clobazam (n=43): 95% at 3 months, 80% at 6 months, 74% at 9 months, and 69% at 12 months. Adverse events (AEs) were recorded in 14/43 (33%) patients, most commonly diarrhoea (7%) and somnolence (5%). Serious AE incidence: 7%. No patients discontinued CBD due to an AE after 3 months. Elevated liver enzymes were reported at least once during the study for 2 patients with LGS (1 adult, 1 paediatic).

Conclusion: Interim results from this retrospective study indicate favourable retention on CBD without concomitant clobazam for up to 12 months in patients with LGS or DS in clinical practice. These preliminary findings trend towards favourable effectiveness of CBD independent of clobazam.

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Quantitative EEG analysis during the MONARCH Phase 1/2 study of STK-001, an antisense oligonucleotide (ASO), in Dravet syndrome (DS)

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Rationale: DS is a severe, progressive, and genetic epilepsy typically caused by heterozygous loss of function mutations in the SCN1A gene encoding the voltage-gated sodium channel type 1 α subunit (Na1.1). We performed quantitative EEG analysis on recordings from the MONARCH study of STK-001, an investigational ASO treatment designed to upregulate Na1.1 protein expression.

Methods: MONARCH (NCT04442295) is an ongoing study of patients with DS aged 2-18y receiving single or multiple ascending doses of STK-001. We analyzed 1-2h EEGs collected at baseline, 12w and 24w post-treatment. Interictal epileptiform discharges (IEDs) were detected in the EEG and the spike rate per hour was computed. Spectral power analysis was performed in the delta, theta, alpha, beta, and gamma bands to assess peak frequency and mean power over time.

Results: Spikes were detected in only 7/24 recordings (29%) obtained from 12 patients. Spectral analysis of 19 1h recordings at baseline revealed a mean alpha/theta power ratio over time of <1 across age groups (0.73±0.19SD in 2-12y and 0.85±0.24SD in 13-18y). With doses above 10mg, 6/8 and 7/8 patients in the 2-12y group showed decreases in mean theta and alpha over time, respectively, between baseline and 12w post-treatment. Subsequently, 3/4 and 4/4 patients re-increased towards baseline at 24w post-treatment. No trends were observed in theta or alpha peak frequency between baseline and 12w post-treatment (n=19).

Conclusions: Spike analysis of 1-2h EEGs in this cohort seems not informative as spikes were detected in too few recordings to draw conclusions. Greater theta compared with alpha power in younger and older age groups is consistent with prior data showing increased theta and decreased alpha in children with DS after 6y compared with controls (Holmes et al 2012). Initial trends indicate modulation of theta and alpha power may be a useful tool following treatment with STK-001.
Assessment of the unmet medical needs for patients with Lennox-Gastaut syndrome: a survey in collaboration with the European Collaboration for Epilepsy Trials Consortium

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Purpose: Lennox-Gastaut syndrome (LGS) is a rare, treatment-resistant epileptic and developmental encephalopathy characterized by high burden of multiple seizure types. This survey was undertaken to assess the current state of care of LGS patients and identify unmet needs in Europe.

Methods: In September 2021, in collaboration with Zogenix, the European Collaboration for Epilepsy Trials (ECET) Consortium (https://epi-care.eu/european-collaboration-for-epilepsy-trials/) conducted a questionnaire survey. Specialized centers with expertise in rare and complex epilepsies were identified and recruited to participate. The survey requested information regarding the number and ages of LGS patients, the number of anti-seizure medications (ASMs) used or previously tried, and the anti-seizure effectiveness of current treatment. Each center also ranked 11 goals of treatment in order of importance.

Results: 61 centers, including European Reference Network EpiCARE reference centers, from 23 countries participated in the survey. 75% of the centers managed ≥15 LGS patients; 36% managed only children, and 18% managed only adults. Seizure-related goals of treatment (eg, seizure-freedom, fewer drop seizures, etc.) were ranked as being the most important by 66% of centers, followed by quality-of-life improvements by 18% of centers. Nearly 90% of centers reported that more than half of their patients experienced breakthrough seizures each month, and 38% of centers reported that >50% of their patients experience monthly drop seizures. The difficulty in managing LGS patients was illustrated by the fact that 69% of centers try 5-10 ASMs and 18% of centers try >10 ASMs in their search for an effective regimen for each patient. Nearly all centers (98%) indicated an unmet need exists for effective ASMs to treat LGS patients, and 87% of centers voiced support for new ASMs with novel mechanisms of action.

Conclusions: The responses to this survey support the existence of unmet therapeutic needs for the treatment of LGS.

Sponsor: Zogenix International Limited.

The impact of disease severity on efficacy from a Phase 2b study of XEN1101, a novel potassium channel opener, in adults with focal epilepsy (X-TOLE)

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Purpose: X-TOLE was designed to assess the efficacy and safety of XEN1101 in adults with focal onset seizures (FOS).

Methods: X-TOLE was a double-blind, placebo-controlled, dose-ranging study. Subjects had ≥4 FOS per month, recorded with an eDiary, and stable treatment with 1-3 antiseizure medications (ASMs).

Results: A total of 325 subjects were randomized and treated across three treatment groups or placebo in a 2:1:1:2 ratio (25 mg: 20 mg: 10 mg: placebo). Overall, XEN1101 demonstrated a dose-dependent reduction from baseline in median monthly FOS frequency of 33.2% (p=0.035, n=46), 46.4% (p<0.001, n=51), and 52.8% (p<0.001, n=112) in the 10mg, 20mg, and 25mg groups, respectively, compared to placebo (18.2%, n=114). X-TOLE included a “difficult-to-treat” patient population given baseline seizure burden, number of prior failed antiseizure medications, and number of concomitant ASMs during the study. The median seizure frequency was 13.5/month at baseline; 50.8% study subjects were taking 3 concomitant ASMs; and median number of ASMs taken prior to study entry was 6. The followinpost hoc analyses were completed to understand the role of disease severity and pertain to the 25 mg treatment group. Compared with baseline, subjects with ≤8.5 seizures/month at baseline experienced a 70.6% reduction compared to 50.8% for those with >8.5 seizures/month. Median monthly FOS reduction was 58% in subjects who failed ≤6 ASMs at baseline and 43% in subjects who failed >6 ASMs. Median monthly FOS reduction was 60.9% for subjects with 1-2 concomitant ASMs and 50.8% for subjects with 3 concomitant ASMs.

Conclusion: X-TOLE met the primary and key secondary efficacy endpoints with XEN1101 demonstrating a statistically significant, dose-dependent reduction in monthly FOS frequency compared to placebo in a difficult-to-treat population. These post hoc analyses suggest that efficacy may be more robust in patients with less severe disease, which mirrors likely use of XEN1101 if approved.
Rapid onset of efficacy of XEN1101, a novel potassium channel opener, in adults with focal epilepsy: results from a phase 2b study (X-TOLE)

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Purpose: This Phase 2b study was designed to assess the efficacy and safety of XEN1101 in focal onset seizures (FOS). XEN1101 is a novel, potent, selective KCNQ2/3 (Kv7.2/7.3) potassium opener being developed for FOS and major depressive disorder. Its pharmacokinetic properties support once daily oral dosing without titration.

Methods: X-TOLE was a double-blind, placebo-controlled, dose-ranging study. Subjects had ≥4 FOS per month, recorded with an eDiary, and stable treatment with 1-3 antiseizure medications (ASMs).

Results: A total of 325 subjects were randomized and treated across four treatment arms in a 2:1:1:2 ratio (25mg: 20mg: 10mg: placebo). XEN1101 demonstrated a dose-dependent reduction of 33.2% (p=0.035, n=46), 46.4% (p<0.001, n=51), and 52.8% (p<0.001, n=112) in the 10mg, 20mg, and 25mg groups, respectively, from baseline in median monthly FOS compared to placebo (18.2%, n=114).

A prespecified weekly assessment of seizure frequency was conducted followed by a post hoc statistical pair-wise comparison between placebo and each treatment. At week 1, XEN1101 demonstrated a dose-dependent reduction of 39.1% (p<0.01), 41.5% (p=0.04) and 55.4% (p<0.001) in the 10mg, 20mg, and 25mg groups, respectively, from baseline in median FOS compared to placebo (20.2%).

Conclusion: X-TOLE met the primary and key secondary efficacy endpoints with XEN1101 demonstrating a statistically significant, dose-dependent reduction in monthly FOS frequency compared to placebo. Consistent with lack of need for titration, there was a marked reduction in median FOS at week 1 in all doses compared with placebo. The rapid onset and sustained efficacy remain to be confirmed in Phase 3. XEN1101 may offer a compelling option for patients seeking an adjunctive therapy that quickly provides additional seizure reduction.

Patients’ perspectives on reasons for variable adherence to antiseizure medications

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Purpose: Patients with epilepsy most often use antiseizure medications (ASMs) over a long time. We have previously shown that both intentional and non-intentional adherence may be a challenge in the treatment. Thus, we wanted to explore the patients’ experience and perspectives on reasons for variable adherence.

Method: An online questionnaire was open to patients through the website of the Norwegian Epilepsy Association, from April 1st to September 5th 2017. All responders were anonymous, and therefore approval from the Regional Ethics committee was not needed. One question contained open space for answers, to give the responders the opportunity to elaborate on reasons for variable adherence: “What is the reason why you take your medications otherwise that as agreed upon with your treating physician?” The answers were handled in a mixed-model way, categorized and discussed semi-quantitatively and through systematic text condensation.

Results: There were 1150 responders (778 women/372 men), aged 11-83 years, and 157 patients replied to this specific question with elaborating information based on the questionnaire various reasons were stated and described. The answers were categorized into 10 subgroups through systematic text condensation. One main category included patients who forgot to take their medication (40%). Other explanations included drug intake at another time than prescribed (17%), drug intake or timing not fitting into everyday routines (10%), dosage adjustments without consulting treating physician (8%), fear for seizures (5%), changed sleeping pattern, intake of alcohol, resistance to medications and other (<5% in each category). The answers provide a nuanced picture of reasons to variable adherence.

Conclusion: More focus on the patients’ perspectives on adherence to treatment in epilepsy highlight the need for improved understanding of their experiences of use of ASMs as a way forward to improve treatment, communication and health literacy among patients and health care workers.
Oxcarbazepine and hyponatremia

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Purpose: Hyponatremia is one of the most common adverse effects in patients treated with oxcarbazepine (OXC). Different risk factors for OXC-induced hyponatremia have been described (e.g., age, dosage, combination with other drugs, female gender). During our clinical practice, we have noticed that longer duration of treatment with OXC could be associated with higher risk of hyponatremia, therefore, in this study we aimed to evaluate the factors that may increase risk of OXC-induced hyponatremia.

Method: Thirty-one adult patients with epilepsy who received OXC monotherapy or combination therapy were retrospectively included in this study. The following data were collected: demographic information (gender, age), clinical characteristics (OXC, sodium concentration, duration of OXC therapy, comedication). Individuals who had another condition that could potentially affect sodium levels (e.g., pregnancy, use of diuretics, adrenal gland insufficiency and hypopituitarism) were excluded. Hyponatremia was defined as <136 mmol/l.

Results: The data of 31 patients was analyzed (64.5% females [n=20]; median age 50 years with a range of 20-77 years). The daily dose of OXC ranged from 300 to 1950 mg and its median was 1200 mg. The average serum concentration of OXC was 15.4 ± 6.3 µg/ml (reference range 10-35 µg/ml). OXC as monotherapy was used by 8 (25.8%) participants. Median duration of OXC therapy was 8 years with a range from 1 to 22 years. The majority of patients (61.3%, n=19) developed hyponatremia. Binary logistic regression analysis demonstrated that each year of therapy with OXC increased hyponatremia risk 1.403 times (OR=1.403, 95% CI 1.048-1.879, p=0.023) whereas other factors (gender, age, polypharmacy, OXC dosage and serum concentration) did not show significant association with the development of hyponatremia.

Conclusion: Longer duration of treatment with oxcarbazepine is associated with a higher risk of hyponatremia.

ELEVATE Study 410: perampanel as monotherapy or first adjunctive therapy in patients with focal-onset seizures or generalised tonic-clonic seizures: analysis by patient age

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Purpose: Here we present final efficacy and safety from ELEVATE (Study 410; NCT03288129), a multicentre, open-label, Phase IV study of perampanel monotherapy or first adjunctive therapy in patients aged ≥4 years with focal-onset seizures (FOS), with/without focal to bilateral tonic-clonic seizures, or generalised tonic-clonic seizures (GTCS), by age (12 to < 18, 18-64 and >64 years).

Method: The study comprised Screening, Titration (≤13 weeks), Maintenance (39 weeks) and Follow-up (4 weeks) Periods. Patients received 2 mg/day perampanel up-titrated to 4 mg/day (dose increases [by 2 mg] based on response and tolerability; maximum, 12 mg/day). Primary endpoint: retention rate over 12 months; secondary endpoints: seizure freedom (Maintenance) and safety; exploratory endpoints: median percent reduction in seizure frequency/28 days and 50% responder rate during Maintenance.

Results: The Safety Analysis Set included 54 patients and the Full Analysis Set included 52 patients. Four patients were aged 12 to <18 years (FOS, n=1; GTCS, n=3); 44 were aged 18-64 years (FOS, n=31; GTCS, n=8; FOS+GTCS, n=5); and six were aged >64 years (FOS, n=6). Retention rates at 12 months were 50.0% (n=2/4) in the 12 to <18 age group, 65.9% (n=29/44) in the 18-64 age group and 50.0% (n=3/6) in the >64 age group. Seizure-freedom rates, 50% responder rates and median percent reduction in seizure frequency, respectively, were 50.0% (n=2/4), 75.0% (n=3) and 76.7% (n=4) in the 12 to <18 age group, 33.3% (n=14/42), 67.9% (n=30/45) and 37.7% (n=3) in the 18-64 age group, and 16.7% (n=1/6), 100.0% (n=4/4) and 94.3% (n=4) in the >64 age group. Treatment-related treatment-emergent adverse events were reported by 63.0% of patients across age groups.

Conclusion: ELEVATE found perampanel as monotherapy or first add-on therapy was generally well tolerated across all age groups and seizure types. Improvements in seizure frequency were observed regardless of age.

Funding: Eisai Inc.
Cannabidiol use in a patient with multiple comorbidities

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Purpose: Cannabidiol was approved by the FDA and EMA in 2018 and 2019 respectively and is effective for seizure control in patients with Dravet syndrome, Lennox-Gastaut syndrome (LGS), and Complex Tuberous Sclerosis. Its mechanism of action is not totally known but its metabolism leads to interaction with several antiepileptic drugs, in particular Clobazam. The most common adverse effects are hepatocellular damage, sedation, suicidal ideation, hypersensitivity. (Franco et al, Neuropharmacology 185, 2021).

Method: We present the case of a 27-year-old patient suffering from LGS; history of tricuspid atresia with a single ventricle, prolonged cardiac arrest during cardiac surgery at birth, cognitive impairment, hepatopathy. He presents polymorphic seizures, tonic, atonic with fall, atypical absences resistant to numerous pharmacological trials (total 90 seizures/month); EEG characteristic for LGS. Current therapy: Carbamazepine, Clobazam.

Cannabidiol was gradually introduced and, having reached 12.5 mg/kg/day, Clobazam was gradually reduced. In consideration of the known hepatopathy, close monitoring of liver function indices and ultrasound was performed in collaboration with the hepatologist specialist.

Results: The introduction of cannabidiol resulted in a 45% reduction in seizure frequency; no hepatic or behavioral adverse effects were reported.

Conclusion: The association of cannabidiol and clobazam leads to an increased antiepileptic effect at the cost, however, of an increased risk of adverse effects (Baier, et al, Epilepsia, 61, 2020) that must be carefully evaluated and monitored in the individual patient. However, close clinical and laboratory monitoring allows the use of cannabidiol even in patients with multiple comorbidities.

Safety and efficacy of third-generation antiseizure medications: real-world data from a multicentric retrospective study

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Purpose: To assess and compare the effectiveness and tolerability of third-generation antiseizure medications (ASMs): brivaracetam (BRV), eslicarbazepine acetate (ESL), lacosamide (LCM) and perampanel (PER), in patients with treatment-resistant epilepsy (TRE).

Method: A multicentric retrospective study collecting data from four Neurology units of Calabria Region (Italy) between January 2019 and July 2021. All outpatients with focalTREwho started one of the four ASMs during the study period, with at least 6 months follow-up, have been included. For each ASM, responder rate (≥50% reduction in seizure frequency), seizure-free rate, dropout rate and patients with treatment emergent adverse events (TEAEs) were assessed.

Results: Data on 318 patients have been collected (52.2%, females, mean age 47.4 years [± 16.8 SD]). Mean duration of illness was23.3 years (± 16.8 SD), with mainly monthly (45.3%) seizures. 39.9% of patients were previously treated with ≥5 ASMs. Most patients were treated with LCM (37.1%), followed by ESL (21.1%), PER (23.3%), BRV (18.5%); 62.9% were taking ≥2 concomitant ASMs. At last follow-up available, responder rates were 40.7% (BRV), 34.3% (ESL), 27% (PER), 25.4% (LCM); seizure free rates were 22.4% (ESL), 16.2% (PER), 11% (LCM), 10.2% (BRV). Overall, 11.9% of patients discontinued treatment, mainly due to lack of efficacy (21/38). Dropout percentages were 16.2% (PER), 15.3% (LCM), 7.5% (ESL), 5.10% (BRV). 19.8% of subjects had ≥1 TEAEs, mostly dizziness (31/74); TEAEs rates were 31.1% (PER), 26.3% (LCM), 11.9% (ESL), 1.7% (BRV). No statistically significant differences were found comparing efficacy and safety outcomes among the four treatment groups.

Conclusion: Real-world data from patients with TRE treated with newer ASMs seem to confirm the effectiveness and tolerability of these medications. The small sample size and the large disproportion among the treatment groups did not allow statistically significant comparisons. Therefore, results from larger cohorts and real-life prospective studies are needed.
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ELEVATE Study 410 of perampanel as monotherapy or first adjunctive therapy in patients with focal-onset seizures or generalised tonic-clonic seizures: analysis by first-line enzyme-inducing anti-seizure medication use

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Purpose: ELEVATE (Study 410; NCT03288129) was a multicentre, open-label, Phase IV study of perampanel monotherapy/first adjunctive therapy in patients with focal-onset seizures (FOS), with/without focal to bilateral tonic-clonic seizures (FBTCS), or generalised tonic-clonic seizures (GTCS). Here we present case series of patients who received concomitant enzyme-inducing anti-seizure medications (EIASMs).

Method: The study comprised Screening, Titration (≤13 weeks), Maintenance (39 weeks) and Follow-up (4 weeks) Periods. During Titration, patients received perampanel 2 mg/day, which was up-titrated to ≥4 mg/day (maximum, 12 mg/day). Dose increases were weekly for those taking EIASMs. Primary endpoint: 12 month retention rate; secondary endpoints: seizure freedom and safety; exploratory endpoints: median percent reduction in seizure frequency/28 days.

Results: Overall, 54 patients were included in the Safety Analysis Set; four (7.4%) patients received EIASMs. Of those, two patients discontinued (sudden unexpected death in epilepsy [SUDEP], n=1; subject choice, n=1). Patient 1 (23 year-old male) with FOS received perampanel (last dose 2 mg/day) with concomitant oxcarbazepine and showed 68.7% reduction in seizure frequency during the Maintenance Period. Patient 2 (26 year-old female) with FOS, with FBTCS, received perampanel (last dose 6 mg/day) with concomitant phenytoin and achieved seizure freedom. Patient 3 (13 year-old male) with FOS received perampanel (last dose 6 mg/day) with concomitant oxcarbazepine and achieved seizure freedom. Patient 4 (67 year-old female) with FOS, with FBTCS, received perampanel (last dose 6 mg/day) with concomitant carbamazepine. Patient 4 did not have any seizures during pretreatment and remained seizure free during the study. None of the patients receiving EIASMs reported severe adverse events, except the event of SUDEP (unrelated) in Patient 3.

Conclusion: ELEVATE suggests perampanel as first adjunctive therapy was efficacious and generally well tolerated in four patients receiving concomitant EIASMs; further investigation is warranted due to the small sample size.

Funding: Eisai Inc.

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Effect of number of concomitant anti-seizure medications at baseline on efficacy and safety outcomes from a mirroring clinical practice study of perampanel in adults and adolescents

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Purpose: A Mirroring Clinical Practice Study in Italy (AMPA; NCT04257604) was a multicentre study that evaluated the effectiveness and safety of adjunctive perampanel in adult and adolescent patients with focal-onset seizures (FOS, with/without focal to bilateral tonic-clonic seizures). Here, we present results from a post hoc analysis by number of concomitant anti-seizure medications (ASMs) at baseline (1, 2 or ≥3).

Method: Patients (aged ≥12 years) with insufficiently controlled seizures while receiving 1–3 ASMs were prescribed adjunctive perampanel per the approved indication. Seizure diaries and treatment-emergent adverse events (TEAEs) were verified at study visits (baseline and after 3/6/12 months of treatment). Primary endpoint: percentage change from baseline in seizure frequency/28 days at Month 6 (secondary endpoint, Month 12); other secondary and safety endpoints: 50% and 75% responder, seizure-free and retention rates and TEAEs over 12 months.

Results: Overall, 234 patients received adjunctive perampanel (Safety Analysis Set). At baseline, patients received 1 (21.6% [n=50/232]), 2 (44.4% [n=103/232]) or ≥3 (34.1% [n=79/232]) concomitant ASMs (two patients taking no concomitant ASMs were excluded); carbamazepine and levetiracetam were most commonly taken. Median percent reductions in seizure frequency were 63.3%, 50.0% and 56.5% at Month 6, and 77.9%, 63.9% and 69.2% at Month 12 for patients receiving 1, 2 and ≥3 concomitant ASMs, respectively. 50% and 75% responder, seizure-freedom and retention rates, respectively, at Month 12 were 71.4%, 52.4% and 56.0% for patients receiving 1 concomitant ASM, 59.8%, 40.2%, 20.2% and 58.3% for patients receiving 2 concomitant ASMs, and 63.8%, 44.9%, 13.0% and 57.0% for patients receiving ≥3 concomitant ASMs. TEAE incidence was 58.0%, 58.3% and 51.9% for patients receiving 1, 2 and ≥3 concomitant ASMs, respectively.

Conclusion: Adjunctive perampanel was efficacious and generally well tolerated in adult and adolescent patients with FOS regardless of number of concomitant ASMs at baseline.

Funding: Eisai s.r.l.
Cumulative plasma concentration exposure, not singular concentrations, best explains the correlation for brivaracetam and levetiracetam to photoparoxysmal response elimination in patients with photosensitive epilepsy: updated exploratory results from a randomized, double-blind, crossover study

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Purpose: Brivaracetam-BRV i.v. was 61% faster ($p=0.039$, median=5.5 min) to elimination of EEG PPR than an equi-potent i.v. Levetiracetam-LEV in a previously conducted study in 9 patients with epilepsy(PwE)+photosensitivity (Reed, CNS Drugs 2020). Herein, we retrospectively explored the relationship of anti-seizure medications-ASM plasma concentrations to time to PPR elimination.

Methods: Study design details have been stated previously (Reed et al.), where Part 1=1500 mg LEV, 100 mg BRV post-15-min i.v. and Part 2=same ASM doses at-5-min i.v. All patients had Hx GTCS, myoclonic seizures, or both. All serial plasma LEV, BRV samples were stored at ≤-20 degrees C; plasma [BRV], [LEV] analysis via LC-MS/MS. The lower limit of quantification for BRV=0.1 mcg/mL (10 ng/ml), and LEV=1.0 mcg/mL; within- & between-day coefficient of variation (%CV), low [BRV] concentration=3.1&2.9%, respectively; LEV=8% for both. All natural log (Ln) Area-Under-the-plasma-Concentration-time-curves (AUC, or exposure) were calculated using a linear trapezoidal method. Plasma correlation plots were constructed via least-squares multiple linear regression and $p$ values via Excel.

Results: Nine PwE (6F; age=27.8[18-42]yr) completed, with PPR elimination (31/32 instances). A greater BRV:LEV difference in PPR elimination was observed for 15-min infusions vs. 5-min, with greater variability in Part 2. At PPR elimination (n=16), median plasma [BRV]=250 (range=30-1,100) ng/ml; [LEV]=28.35 [range 1-86.7] mcg/mL. For Parts 1 & 2 separately, then combined, very strong Pearson correlation coefficients ($r$) were observed when plotting time to PPR elimination versus LnAUC for both LEV and BRV, whereas singular Ln[BRV] or Ln[LEV] did not correlate well, except for [BRV] in Part 1 (see Table).

Conclusion: Cumulative Ln plasma [BRV] and [LEV] concentration-exposure best correlates to elimination of the pharmacodynamic EEG biomarker of photosensitivity (PPR) in the majority of PwE. Singular Ln plasma concentrations do not correlate well. Frequent plasma samples are needed when evaluating ASM compounds in the ‘Photosensitivity Model of Epilepsy’ to calculate cumulative [ASM] exposure.
Study 512 design: a prospective, observational, multicentre study of perampanel as first adjunctive therapy in routine clinical care of patients aged ≥12 years with focal-onset seizures or generalised tonic-clonic seizures associated with idiopathic generalised epilepsy

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**Purpose:** Patients with uncontrolled seizures while on antiseizure medication (ASM) monotherapy may require adjunctive therapy. Perampanel is a once-daily oral ASM authorised as an adjunctive treatment for partial-onset seizures (POS), with/without secondarily generalized seizures (SGS), in patients aged ≥4 years; and for primary generalised tonic-clonic seizures (PGTCS) in patients aged ≥7 years with idiopathic generalised epilepsy (IGE). Study 512 (NCT04252846) is a prospective, observational, multicentre study to assess the dosage, effectiveness and safety of perampanel as adjunctive therapy in patients aged ≥12 years with uncontrolled POS or PGTCS in clinical care in Europe. Herein, we present the design of Study 512.

**Method:** Enrolled patients received perampanel as the first adjunctive therapy to ASM monotherapy per the investigator’s decision. Key inclusion criteria: aged ≥12 years; diagnosis of epilepsy (POS [with/without SGS] or PGTCS with IGE); uncontrolled seizures with ≤2 ASM monotherapies; available baseline seizure-frequency data. Key exclusion criteria: episode(s) of status epilepticus in ≤6 months pre-Screening; ≥2 ASMs in combination (except for cross-titration between ASM monotherapies); previous/current perampanel use. Patients will be assessed at baseline and as per routine clinical care, with study visits occurring at 6 and 12 months post-baseline. The primary outcome is 12-month retention rate. Secondary outcomes include: 6-month retention rate; change in seizure frequency and responder/seizure-freedom/seizure-worsening rates at 6 and 12 months; dosing patterns; treatment duration; and safety. Descriptive statistics will be used for analysis.

**Results:** Study 512 enrolled approximately 300 patients (PGTCS and aged 12-<18/≥65 years, each n≥50) at 40 study sites across 5 countries between July 2020 and December 2021. A final enrolment update will be presented in the poster.

**Conclusion:** Study 512 will provide prospective, observational data on the real-world use of perampanel as first adjunctive therapy in patients aged ≥12 years with epilepsy.

**Funding:** Eisai Inc.; Eisai Ltd.; Eisai Co., Ltd.
Effect of sex on efficacy and safety outcomes from a mirroring clinical practice study of perampanel in adults and adolescents

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Purpose: A Mirroring Clinical Practice Study in Italy (AMPA; NCT04257604) was a multicentre study that evaluated the effectiveness and safety of adjunctive perampanel in adult and adolescent patients with focal-onset seizures (FOS, with/without focal to bilateral tonic-clonic seizures [FBTCS]). Here, we present results from a post-hoc analysis stratified by sex.

Method: Patients (aged ≥12 years) with insufficiently controlled seizures while receiving 1–3 anti-seizure medications were prescribed adjunctive perampanel per the approved indication. Seizure diaries and treatment-emergent adverse events (TEAEs) were verified at study visits (baseline and after 3/6/12 months). The primary endpoint was median percent change from baseline in seizure frequency per 28 days at Month 6 (secondary endpoint, Month 12); other secondary endpoints: 50% and 75% responder rates, seizure-freedom rates, retention rates and monitoring of TEAEs up to 12 months.

Results: In total, 234 patients received adjunctive perampanel and were included in the analysis; 48.7% (n=114/234) were males and 51.3% (n=120/234) were females. Median percent (95% confidence interval [CI]) change from baseline in seizure frequency was 55.0% (39.1%–66.7%) for males and 55.7% (42.7%–75.4%) for females at Month 6 and 65.3% (51.0%–71.4%) for males and 74.8% (58.8%–83.5%) for females at baseline in seizure frequency per 28 days at Month 6 (secondary endpoint, Month 12). The 50% and 75% responder rates at Month 12 were 61.5% and 38.5%, respectively, for males and 65.4% and 50.0%, respectively, for females. Seizure-freedom rates were 19.6% and 18.1%, and the retention rates were 56.1% and 58.3%, for males and females, respectively. Overall TEAE incidence was 56.1% for males and 56.7% for females. Most common TEAEs were dizziness/vertigo (20.2%) and irritability (8.8%) in males and dizziness/vertigo (23.3%) and somnolence (10.8%) in females.

Conclusion: These results suggest that adjunctive perampanel is efficacious and generally well tolerated in adult and adolescent patients with FOS (with/without FBTCS) regardless of sex.

Funding: Eisai s.r.l.

Final results of Study 505, a post-marketing surveillance study of perampanel film-coated tablets and oral suspension in Korean patients

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Purpose: Here, we present final results of Study 505 (NCT02722590), a post-marketing surveillance study of perampanel film-coated tablets and oral suspension in Korean patients with focal-onset seizures (FOS), with/without focal to bilateral tonic-clonic seizures (FBTCS), aged ≥4 years, or with generalised tonic-clonic seizures (GTCS) in patients aged ≥7 years.

Method: Patients who met the approved indication for perampanel were eligible for inclusion: monotherapy (film-coated tablets) for FOS, with/without FBTCS; adjunctive therapy (film-coated tablets/oral suspension) for FOS, with/without FBTCS, or GTCS. Patients received perampanel (film-coated tablets/oral suspension) once daily and were monitored up to 24 weeks from the first dose or for 4 weeks after discontinuation. Patients who received ≥1 dose of perampanel with safety information were included in the Safety Analysis Set (SAS). Safety assessments included monitoring of adverse events (AEs). Efficacy was measured by the Investigator’s Clinical Global Impression of Change (CGI-C; seven-point scale from 1 [very much improved] to 7 [very much worse]) up to 24 weeks in patients from the SAS who received perampanel for ≥12 weeks (Efficacy Analysis Set).

Results: Study 505 was completed on 9 July 2021. For film-coated tablets, 3354 patients were in the SAS and 1819 were in the Efficacy Analysis Set. For oral suspension, five patients were in the SAS and none were in the Efficacy Analysis Set. Of the patients taking the film-coated tablets, 1094 (32.6%) experienced AEs, the most common being dizziness (12.8%). No AEs were reported in patients taking oral suspension. For patients taking film-coated tablets, CGI-C was minimally, much or very much improved for 1253/1819 (68.9%) patients in total and 902/1235 (73.0%) patients treated with perampanel for ≥24 weeks.

Conclusion: Results from Study 505 suggest that perampanel film-coated tablets are generally well tolerated and effective in a routine clinical practice setting in Korea.

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Real-life experience of brivaracetam in focal to bilateral and primary generalized tonic-clonic seizures

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Purpose: Brivaracetam (BRV) is an antiseizure medication (ASM) indicated for focal onset seizures. It has shown efficacy in focal to bilateral tonic-clonic seizures (FBTCS). However, its efficacy in primary generalized tonic-clonic seizures (GTCS) is unknown. The aim of this study is to determine real-life efficacy and safety of BRV in patients with FBTCS and GTCS.

Methods: We performed a multicenter retrospective longitudinal study including adult patients with a definite epilepsy diagnosis that had at least one FBTCS or GTCS prior to starting BRV. Data was collected from the consecutive outpatient visits during a period of 3 years. All patients needed a follow-up of 3 months prior to starting BRV (baseline visit) and completed a minimum follow-up of 3 months after starting BRV (follow-up visit). Efficacy was based on the FBTCS or GTCS frequency during the 3 months prior to the final visit compared to the 3 months before baseline visit.

Results: 123 patients were included (mean age 36.3 ± 18.0; 48% female), of which 94 had a 12-month follow-up period. 63.4% were FBTCS and 36.6% were GTCS. At 12 months of follow-up, monthly FBTCS and GTCS frequency decreased significantly (median 0 vs 0.3; p < 0.001). The responder rate (patients with a reduction of > 50% of FBTCS or GTCS frequency) was 83%. 73.4% were free of FBTCS or GTCS after 12 months. Retention rate was 79% at 12 months. 29.8% of patients suffered adverse effects, the most common being drowsiness (14.9%). There was a higher rate of seizure freedom in patients with FBTCS than in GTCS (80.7% vs 62.2%; p < 0.05).

Conclusion: BRV is an effective and well-tolerated ASM in patients presenting tonic-clonic seizures, so it can be a suitable treatment option in adult patients with both FBTCS and GTCS.

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The effects of some Stachys l. and Teucrium l. species growing in Turkey in the pentylenetetrazol (PTZ) model of seizures

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Purpose: Stachys and Teucrium taxa have been traditionally used for the treatment of many disorders, including epilepsy. The preclinical studies on the anticonvulsive effects of these species are very limited (1-4). The aim of the study is to evaluate the anticonvulsive activity of some Stachys and Teucrium species with in vivo model.

Method: The dried aerial parts of Stachys byzantina, Stachys officinalis, Stachys cretica subsp.anatolica, Teucrium chamaedrys subsp. chamaedrys and Teucrium montanum were extracted with the mixture of ethanol:water(70:30). The anticonvulsant activity of the aqueous ethanolic extracts of the species was investigated in the Pentylenetetrazol (PTZ) model of seizures in BALB-C albino mice. Aqueous ethanolic extracts of species (50 mg/kg (only T. montanum), 100 mg/kg and 200 mg/kg) and isotonic saline solution as a control group were administered intraperitoneally (i.p.), before the induction of seizures by PTZ (80 mg/kg,i.p.) and then the overall seizure score and the latency to first myoclonic seizure evaluated.

Results: The results demonstrated a significant increase in latency to PTZ-induced myoclonic seizures at the doses of 100 mg/kg (60 ±2.62 s) and 200 mg/kg (60,17 ±2.66 s) S. byzantina extract and 50 mg/kg (59,83 ±2,4) T. montanum extract compared to control group (42,17 ±3,32) (p< 0.05*). Moreover, 200 mg/kg of S. byzantina extract significantly decreased the overall seizure score compared to the control (p< 0.05*).

Conclusion: These results showed that especially extract of Stachys byzantina exhibited significantly effective anticonvulsant properties. This is the first study presenting the anticonvulsant potential of these taxa.

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Cannabidiol for refractory adult epilepsies: broadening the Lennox-Gastaut phenotype?

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**Purpose:** Cannabidiol has been licensed in the UK for those with refractory seizures associated with Lennox Gastaut Syndrome (LGS). However, characterizing LGS in adults can be challenging. Patients are frequently too agitated to tolerate EEG monitoring. Many patients are monitored by carers whose expertise may be variable; identifying seizures, particularly non convulsive manifestations such as atonic head drops or sleep-related tonic seizures, is therefore unreliable. We sought to ascertain whether those with an LGS-type syndrome - refractory multifocal epilepsy with cognitive impairment and multiple seizure types arising in childhood, would benefit from Cannabidiol. These patients did not have the typical electroclinical phenotype for LGS.

**Method:** Individual Funding Requests were made for five patients. Four had genetically defined syndromes- Alternating Hemiplegia of Childhood, Batten’s disease (CLN5), CHD2 related epileptic encephalopathy and Tuberous Sclerosis. One had Febrile Related Epilepsy Syndrome (FIRES) of unknown etiology. Patients were commenced on adjunctive Cannabidiol between March and December 2021. All patients were prescribed Clobazam.

**Results:** Cannabidiol at a maximum dose of 5mg/kg lead to significant seizure reduction (>50%) in 3 patients. Our patient with Tuberous Sclerosis was the only one who did not experience a reduction in seizure intensity.

**Conclusion:** Cannabidiol is potentially efficacious in adult patients with severe refractory epilepsy 'outside' the typical LGS phenotype.

Clustering of anti-seizure medication prescription sequences from US claims data

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**Purpose:** Patients with epilepsy who do not successfully respond to an Anti-Seizure Medication (ASM) are typically prescribed with different ASM(s) until an effective/appropriate ASM(s) is found to provide an optimal balance between seizure reduction and severity of side-effects. This work is focused on unraveling dominant patterns of prescribed ASM sequences throughout a patient’s medication journey.

**Methods:** We analyzed the US medical insurance claims data for a window of 5 years and identified newly diagnosed epilepsy patients. We included those who had a diagnosis code related to epilepsy or seizure and received their first ASM in the second six month of our window. We excluded those who had an ASM claim in the first six months or a change in their ASM in the last six months or their medication duration was less than 4 years. Finally, we assembled regimens of mono and poly therapies. We identified clusters of ASMs to quantify if an ASM is prescribed, at which part of the medication journey it is more likely to be prescribed. Thus, for each ASM, we computed a sequence of probabilities of being redeemed as the ith-line treatment. We parameterized the probabilities and executed a k-means clustering algorithm to identify representative clusters of ASMs.

**Results:** This cohort consisted of 43,031 patients with a total of 2,378,349 claims from which we assembled 106,381 regimens. We identified three clusters of ASMs: the first consisted of those that, if prescribed, were more probable to be prescribed at the beginning of the journey, the second at the middle of the journey and the third at the end of the journey.

**Conclusions:** The medical claims can identify data-driven models of ASM prescription profiles and has the potential to identify optimal ASM sequences.
First experience with cenobamate in children and adolescents

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Purpose: Cenobamate (CNB), an allosteric GABA<sub>A</sub> ion channel modulator and voltage-gated sodium channel inhibitor, was recently approved as an anti-seizure medication (ASM) to treat adults with focal-onset epilepsy. While promising results exist for adults, there is no experience in its off-label use in pediatric epilepsy patients.

Methods: We evaluated retrospectively the dosing, short-term treatment effect and side effects of CNB in 16 children and adolescents with epilepsy.

Results: Here we report the off-label treatment of 16 pediatric patients with CNB. We specifically describe our experience with CNB dosing in children and adolescents and drug levels of other ASMs. Besides the primary endpoint of seizure control, we examine the specific occurrence of adverse effects.

Conclusion: The results of this study represent a first experience with dosing and safety of CNB in pediatric epilepsy patients. Moreover, we further highlight a positive effect on seizure control in this epilepsy population.

Long-term post-marketing experience with Brivaracetam in epilepsy treatment: longitudinal multicentre study with up to 5 years of follow-up

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Purpose: To evaluate the long-term efficacy, retention, and tolerability of add-on brivaracetam (BRV) in clinical practice

Method: A German multicenter, retrospective cohort study recruited all patients who initiated BRV between February and November 2016, with observation until February 2021.

Results: Data of 262 patients (mean age 40 years, range 5-81, 129 men) were analyzed, including 227 (87%) diagnosed with focal epilepsy, 19 (7%) with genetic generalized epilepsy, and 16 (6%) with another or unclassified epilepsy syndrome. Only 26 (10%) never received levetiracetam whereas 133 (50.8%) were switched from levetiracetam. The length of BRV exposure ranged from 1 day to 5 years with a median retention time of 1.6 years, resulting in a total BRV exposure of 6829 months. The retention rate was 61.1% at 12 months with reported efficacy of 33.1% (79/239; 50% responder rate, 23 patients lost-to-follow-up) including 10.9% reported as seizure-free. The retention rate was 50.8% for the entire study period. At the last follow-up, 133 patients were receiving BRV at a mean dose of 222 ± 104 mg (range 25-400), with 52 exceeding the upper recommended dose of 200 mg. Fewer concomitant antiseizure medications and switching from levetiracetam correlated with better short-term responses. None of the investigated parameters correlated with positive long-term outcomes. BRV was discontinued due to insufficient efficacy in 63 (24%) patients, in 29 (11%) for psychobehavioral adverse events, in 25 (10%) for other adverse events, and in 24 (9%) for other reasons.

Conclusions: BRV showed a clinically useful 50% responder rate of 33% at 12 months and high overall retention above 50%, despite 90% of included patients having previous levetiracetam exposure. BRV was well tolerated; however, psychobehavioral adverse events occurred in one out of 10 patients. Although we identified short-term response and retention predictors, we could not identify predictors for long-term outcomes.

Data already published in full
Levetiracetam prophylaxis therapy for brain tumor-related epilepsy (BTRE) is associated with a higher psychiatric burden

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Purpose: Brain tumor-related epilepsy (BTRE) is a condition characterized by the development of seizures in the context of an undergoing oncological background. Some authors indicate that the high incidence of BTRE justifies the use of prophylactic anti-seizure medications (ASM). Levetiracetam (LEV) is a third-generation ASM widely used in BTRE prophylaxis. The study aims to evaluate LEV neuropsychiatric side effects in BTRE prophylaxis.

Method: Twenty-eight patients with brain tumors were consecutively selected from 2017 to 2019 and divided into two groups: patients with an ascertain diagnosis of BTRE on anti-seizure treatment (BTRE group) and patients with a brain tumor who never had epilepsy and were on prophylactic anti-seizure treatment (PROPHYLAXIS group). Demographics, clinical, neurophysiological, and neuroradiological data of patients of the two groups were assessed. BTRE features, including seizure type, seizure frequency, and anti-seizure therapy, were also evaluated. Neuropsychiatric side effects (SE) of anti-seizure treatment were monitored using the Neuropsychiatric Inventory Questionnaire (NPI-Q) at the baseline visit and 6-month and 12-month follow-up.

Result: 18 patients in the BTRE group and 15 patients in the PROPHYLAXIS group were included. Compared to the BTRE group, the PROPHYLAXIS group showed a higher incidence and severity of neuropsychiatric symptoms as assessed by the NPI-Q score. According to Linear Mixed Models, a multiplicative effect for the interaction between group-treatment for time (p-value=0.02) was observed. For the caregiver distress score (CDS) only a Time-effect was observed (p=0.001) whereas no additive or multiplicative effect was found. Seizure freedom was observed in 15/17 (88%) patients of the BTRE group.

Conclusions: Prophylactic anti-seizure treatment with LEV is associated with increased neuropsychiatric adverse effects. These results stress the importance of accurate epileptological evaluations in patients with a brain tumor to carefully select the ones who would benefit most from anti-seizure therapy.

Efficacy and safety of adjunctive cenobamate in patients with super-refractory focal epilepsy

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Purpose: To assess the safety and efficacy of cenobamate (CNB) as adjunctive therapy in adult patients with focal onset seizures participating in an early access program.

Method: We prospectively recorded information of all adult patients with focal epilepsy who were treated with at least a single dose of CNB as adjunctive therapy in the early access program. Most of these patients where not eligible to participate in clinical trials. We analyzed adverse effects at 3 and 6 months and responder, seizure free and retention rates at 6 months. Baseline seizure frequency was measured during a 3-month period prior to CNB initiation.

Results: Fifty-eight patients older than 18 years with drug-resistant focal epilepsy were included. Mean epilepsy duration was 28.32 years (5-66 years). Mean number of previous antiseizure medications (ASM) was 9 and mean number of concomitant ASM was 3.24, including sodium channel blockers in 56/58 patients and benzodiazepines in 30/58 patients. Mean dose at 6 months was 182.5 mg/day (range: 75-400 mg/day). Six-month >50% and >90% responder rates were 67.5% (25/37 patients) and 29.7% (11/37 patients) respectively and 5% (2/37 patients) were seizure-free. At 6 months 34/40 patients continued CNB treatment (retention rate 85%). Adverse effects (AEs) were experienced by 36/58 patients during the titration period at 3 months and by 21/39 patients at 6 months. The most common AEs were somnolence, unsteadiness and dizziness. One patient presented rash without systemic symptoms which caused drug withdrawal. Eight of the 58 patients discontinued CNB (3 due to AEs, 2 due to lack of efficacy and 3 due to both).

Conclusion: In our series of patients with super-refractory focal epilepsy cenobamate showed a high efficacy as adjunctive therapy. AEs were the typical of other ASM and lead to CNB withdrawal in 10% of the patients.
**Evaluation of suicidality safety reports in epilepsy patients treated with eslicarbazepine acetate**

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**Purpose:** The risk of suicidality has been considered increased in epilepsy patients under treatment with anti-seizure medication (ASM). To evaluate the association between eslicarbazepine acetate (ESL) (Zebinix, BIAL) and suicidality, a review of safety reports of suicidality received by BIAL was performed.

**Method:** The Master Safety Database of ESL was searched for all valid cases with event terms included in the Standardised MedDRA Query (SMQ) “suicide/self-injury” (broad and narrow terms). Cases were retrieved from the Argus Safety™ database cumulatively from inception until 21-Apr-2021 and classified as “related to the topic of interest”, ‘not related to the topic of interest’, and “insufficient information”.

**Results:** 72 valid cases of suicidality (including 2 cases of intentional overdose, and 1 case of self-injury) were retrieved. 43 cases were considered as ‘related to the topic of interest’, 26 cases with ‘insufficient information’ and 3 cases ‘not related to the topic of interest’. 1 case had a probable relationship to ESL as assessed by BIAL and there was no case with positive rechallenge. Of the 43 retrieved cases with sufficient information, 33 cases reported confounding factors or alternative explanations: at least 2 concomitant ASMs (12 cases), or/and concomitant suspect drugs (9 cases) or/and concurrent psychiatric diseases such as depression in their medical history (24 cases).

**Conclusion:** No causal relationship between therapy with ESL and an increased risk of suicidality could be established from the observed data, due to the low number of identified cases and the alternative explanations or confounding factors in most situations.

**Conflicts of interest:** The study was supported by BIAL.

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**Highly purified cannabidiol for children with Lennox Gastaut syndrome with different aetiology: effect on seizures, EEG, behavioural and adaptive functions**

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**Purpose:** Highly purified cannabidiol (Epidyolex) has been approved by European Medicine Agency in 2019 and by Agenzia Italiana del farmaco in 2021 to treat patients from 2 years with Dravet and Lennox Gastaut Syndrome (LGS). We analyse 7 Italian patients (age range: 8-18 years, mean age: 13 years), included in a preliminary study, treated with Epidyolex in add-on (follow up range:12-24 months, mean follow up: 15 months). 7/7 had LGS diagnosis (based on seizures types, EEG pattern, cognitive dysfunction), due to different aetiology (genetic in 3/7: CHD2, CDKL5, GABRB3 encephalopathy; structural in 2/7: hypoxic ischemic encephalopathy, lissencephaly; unknown in 2/7).

**Methods:** All patients underwent genetic and neuroimaging investigations, if not previously performed. Intellectual disability and behavioural abnormalities were reported in 7/7. At the baseline, seizure frequency (generalized tonic-clonic, tonic, myoclonic seizures, spasms and atypical absences), considering 6 months before cannabidiol initiation, EEG, ECG, blood test results, neurological evaluation were reported. Patients continued concomitant treatment (clobazam in add-on for 7/7). A titration scheme was used: 5 mg/kg to 20 mg/Kg/day. CGI scales were performed (after 1 year).

**Results:** Epidyolex was well tolerated in 6/7 (irritability and behavioural aggravation in GABRB3 patient). Efficacy on seizures was reported for 5/7 (seizures reduction ≥ 75% for 3/7, ≥ 50% for 2/7), for all seizures types. Reduction of EEG abnormalities (≥ 50%) was recorded in 3/7. Better outcome was observed in structural aetiology and CDKL5 encephalopathy. Alertness, emotional functioning, daily life activities improved in 5/7. 5/7 decided to continue the treatment (in 2/7 cannabidiol was stopped for inefficacy).

**Conclusions:** Even though further studies are needed to confirm effect of Epidyolex according to LGS underlying aetiology and to assess efficacy on social and communication skills and quality of life of patients and families, cannabidiol proved efficacy on seizures and behavior and tolerability in most children of our casuistic.
Frequently reported AEs leading to perampanel discontinuation

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Purpose: To evaluate frequently reported AEs leading to Perampanel discontinuation

Method: 31 children and 31 adults aged 7-52 y.o. with refractory epilepsy with added-on Perampanel were included in this study. Common and frequently reported AEs leading to Perampanel discontinuation were accounted. Descriptive statistics were used.

Results:

31 children with epileptic encephalopathy, refractory focal epilepsy with/without intellectual disabilities receiving 1-3 AEDs and 31 adults with refractory focal, generalized epilepsies receiving 2-4 AEDs were included in this study. The mean age was 27.2 y.o. Male/female ratio =1:2. Frequently reported AEs were aggression and irritability. 10 patients had frequently reported AEs(16%). Five patients discontinued Perampanel intake due to AEs (8%). There were 4 cases of AEs (80%) that included aggression and/or irritability due to Perampanel and Levetiracetam interactions. In 1 case- polytherapy with topiramate. Man 30 y.o. with Lennox-Gastaut syndrome without seizure remission since onset at 4y.o. became seizure-free with hostile behaviour. Similar AE he had due to the Levetiracetam add-on with positive effects from antipsychotics. We used antipsychotics during the 3-month up-titration of perampanel with a positive result. The patient continued intake of Perampanel and Levetiracetam without AE, antipsychotics and had seizure freedom. Girl aged 9y.o. with polymicrogyria, epileptic encephalopathy, and intellectual disability discontinued perampanel up-titration due to aggression and irritability without management. Good tolerability of perampanel was estimated in other cases with an individualized approach to dosing, including slower up-titration and bedtime dosing.

Conclusion:

Aggression and irritability are frequent AEs for Perampanel. Perampanel and Levetiracetam interactions were temporary conditions. Adverse events management allowed to achieve seizure freedom in patients with refractory epilepsies.

Spectrum EEG analysis signal to evaluate the sleep quality in pediatric patients with sleep disturbance and drug resistant focal epilepsy treated with adjunctive perampanel

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Purpose: Insomnia is associated with increased high EEG frequencies during NREM sleep as a sign of disruption of cortical networks involved in information processing (i.e., cognitive arousal). Our aim is to evaluate the sleep quality with the spectrum EEG analysis signal in pediatric patients with sleep disturbance and drug resistant focal epilepsy receiving adjunctive perampanel therapy.

Method: We retrospectively analyzed 5 patients aged <12 with sleep disturbance (difficulty in falling asleep and frequent nighttime awakenings) and drug resistant focal epilepsy who received adjunctiveperampanel(dosage range: 2-6mg).Sleepquality and daytime sleepiness were assessed with the sleep diary daytime sleepiness sleep quality was also analyzed with the spectrum analysis of the EEG signal: All data was analyzed at baseline (before Perampanel intake) and after 6 months. Patients with modifications in their baseline AEDs or sleep medications were excluded.

Results: PER as adjunctive antiepileptic therapy induced a reduction of partial seizures frequency from 50% to 75% in 3 (60%) patients and seizure freedom in 2 (40%). No adverse events were reported. All patients (100%) reported sleep improvement with a reduction of the daytime sleepiness on the sleep diary and all subjects (100%) showed a spectrum EEG analysis signal with a decrement of high frequencies during NREM sleep after 3 months of the perampanel intake, with maintenance of the results at 6 months.

Conclusion: Adjunctiveperampanel treatment in pediatric patients with drug resistant epilepsy improved the sleep and reduced the daytime sleepiness after 3 months of the therapy, with maintenance of the results at 6 months. On the basis of our results, Perampanel may be a suitable AED in patients with sleep disturbance, in addition to refractory focal seizures.
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Inadequate pregabalin dosage is insufficient for optimal control of epilepsy with focal seizures and concomitant generalized anxiety disorder

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Introduction: The effectiveness of treatment depends on the adequate dosage of medications. In clinical practice, drugs are often used at too low doses, which results in not achieving optimal levels of clinical improvement.

Aim: The aim of the study was to evaluate the effects of increasing the dose of previously taken pregabalin in a group of patients with epilepsy and generalized anxiety disorder (GAD).

Method: The study involved 993 patients (48 ± 15 years old, 482 women and 451 men). Patients were treated adequately for epilepsy with focal seizures and at the same time treated with pregabalin for concomitant GAD. On initial visit, the mean dose of pregabalin was 159 ± 82 mg / day. During the study period (nine months) the dose of pregabalin was increased every 3 months to mean327 ± 163 mg / day. ICD-10 criteria for diagnosis of GAD were confirmed. The severity of anxiety was assessed with GAD-7 Scale. The neuroimaging result and the last EEG were also assessed. The number of epileptic seizures was monitored before and after increasing the pregabalin dose.

Results: At 9 months reduction in seizure frequency was found. Based on the intention-to-treat analysis, 30.5% (N = 285) of the subjects obtained seizure resolution, and 58.1% (N = 542) of the subjects reduced their seizure frequency by at least 50%. At the beginning of the study, despite pregabalin administration, 60.7% of patients was above the diagnostic threshold for GAD diagnosis, after treatment 1.1% in the group of patients with simple partial seizures(63.4 to 0.7% with complex partial seizures and 65.1 to 1 , 1% with secondary generalized seizures respectively).

Conclusions: Almost 90% of patients with focal epilepsy with concomitant anxiety disorder benefit with adequate dosage of pregabalin.

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The long-term effects of Fenfluramine on European patients with Dravet syndrome and their families: a qualitative analysis

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Purpose: Clinical trial data indicate that fenfluramine (FFA) provides meaningful reductions in seizure frequency and improvements in executive function for individuals with Dravet syndrome (DS). This study sought to assess how FFA treatment affects quality of life of individuals with DS and their families.

Method: Study participants were European parents caring for a child with DS. Caregivers participated in one-on-one semi-structured interviews and asked (on a 7-point Likert scale) whether they noticed changes in a number of their child’s seizure- and non-seizure-related quality of life domains after starting FFA treatment; they were also asked about benefits of FFA treatment to their own lives and for the family unit.

Results: The study was concluded in March 2022, with 25 parent caregivers participating. Average participant age was 47.1yrs, and 16 (64%) of the participants were women. Average age and number of months on FFA of the participants’ children with DS was 11.7yrs (range, 3.0-23.6yrs) and 22.4 months (range, 4.7-55.7), respectively. Caregivers reported improvements in both seizure-related (i.e., reductions in seizure activity, triggers and post-ictal recovery times, and improved post-seizure function) and non–seizure-related (i.e., cognition, focus, alertness, speech, academic performance, behavior, sleep, motor function) quality of life domains after FFA treatment. Caregivers also reported that they had better mood and more time for things they enjoyed, felt less overwhelmed, had better sleep quality, and less personal and family stress. Most (96%) caregivers said they would “very” or “quite likely” recommend FFA to others with DS.

Conclusion: Parents with a child with DS reported many seizure- and non-seizure-related FFA treatment benefits for their child, themselves, and their family. Many reported feeling hope for the first time since the child was born or diagnosed with DS.

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In vitro mRNA expression signature of epileptogenic chemoconvulsants

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Various chemoconvulsants with different mechanisms of action induce epileptogenesis in vivo in rodents and primates. However, the downstream molecular pathways activated by convulsant exposure, leading to secondary epileptogenic pathologies are almost unknown. Our objective was to assess (a) the scope of molecular pathways regulated by different convulsants, (b) similarity in gene regulation between the convulsants and (c) the function and possible contribution of regulated genes to epileptogenic secondary pathologies. Eleven convulsant drugs (4-aminopyridine, amoxapine, bicuculline, chlorpromazine, donepezil, kainic acid, pentylenetetrazol, picrotoxin, pilocarpine, SNC80 and strychinine) were investigated. After determining the highest tolerated dose, rat cortical primary cell cultures were exposed to convulsants for 24 h. On the 16th day in vitro, total RNA was extracted for poly-A enriched RNA sequencing to determine the drug-induced expression signature through analysis of differentially expressed genes using Gene Set Enrichment Analysis and Reactome Pathway Analysis. Sixty-one relevant pathways (p<0.05) were enriched by the chemoconvulsants. Of these, 37 were enriched by at least two drugs. Five drugs enriched most of the overlapping pathways, 4-aminopyridine (11 pathways), amoxapine (17), bicuculline (14), pentylenetetrazol (10) and SNC80 (10). Interestingly, donepezil did not enrich any pathways. The pathways presenting the greatest overlap were those responsible for transcription (5 compounds), regulation of insulin growth factor (5), post-translational protein phosphorylation (5), dissolution of fibrin clot (6), cell transport and signaling (9) and extracellular matrix organisation and degradation (8). After in vivo chemoconvulsant exposure, convulsant-induced gene regulation occurs in parallel with that induced by seizure activity. These data suggest that in animal models of chemoconvulsant—induced epileptogenesis, modulation of both the drug-induced and seizure-induced gene expression is needed to mitigate the development of epileptogenic brain pathologies and reduce the risk of epileptogenesis.

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Epidemiology

24 COVID-19 as a neurological disease in a Latin American hospital

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Purpose: The COVID 19 Pandemic has generated a great burden on society and health systems, within its conglomerate of clinical manifestations, neurological manifestations are one of the least mentioned in this regard, but these represent a large component of associated disability. The objective was to describe the neurological manifestations of patients admitted to a level III health institution during a period of 6 months.

Methods: Descriptive observational study of a cohort of 658 patients with a diagnosis of COVID 19 admitted to hospital areas during the period from January to June 2021.

Results: Based on previous studies, neurological manifestations were classified into three categories: manifestations of the central nervous system (CNS) (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizures), manifestations of the peripheral nervous system (PNS) (taste disturbance, smell disturbance, visual impairment, and neuropathic pain), and muscle manifestations (myositis and rhabdomyolysis). They were divided into 3 age groups under 40 years old, between 40 and 60 years old and those over 60 years old, the largest group of patients was made up of the male gender 74% of the total sample, also the group older than 60 years was the more affected by these clinical manifestations. Neurological manifestations were present in 84% of the study members, being those of the peripheral nervous system area more frequent, showing up in 72% of the total members of the study.

Conclusion: Neurological manifestations have been rejected in COVID 19 patients, being these of the most disabling and limiting in terms of function indexes, the long-term consequences of these affectations are unknown for the moment, we recommend that the group carry out a follow-up long-term of these patients and thus evaluate the consequences of these alterations.
**Sudden death in epilepsy, a cohort study of 10 years of follow-up in an institution in Latin America**

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**Purpose:** Sudden death in epilepsy (SUDEP) is the most common cause of death attributable to the disease itself. Almost all the information on this entity comes from studies carried out in central / northern Europe and the United States, with few reports from Latin America. We present the SUDEP casuistry of the Neurology Medical Unit of our hospital.

**Methods:** We studied a historical hospital cohort, without selection of patients for their severity, with 2401 patients, aged ≥18 years, between January 2010 and December 2020. The causes of death were established through death certificates, forensic autopsies, reports of mortality in hospitals, treating physicians and witnesses to deaths. We calculate the incidence and proportional mortality.

**Results:** We identified 8 definitive SUDEP cases (2 SUDEP-plus), one probable and one possible. Considering only the cases with autopsy, the incidence is 0.48 / 1,000 person-years. Of the deceased, 5 are male and 3 female. The mean age is 45.1 years. The main risk factors were therapeutic non-compliance, alcohol consumption and underlying psychiatric illness. The etiology of epilepsy was remote symptomatic or cryptogenic. It is noteworthy that none of the deceased was in remission according to the electroencephalographic records and controls in the medical history.

**Conclusions:** We consider that the incidence and proportional mortality of SUDEP in our study are similar to those found in population-based studies. The risk factors for SUDEP found in our patients are consistent with those recognized in the literature.

**Prevalence of rare and complex epilepsies among adult patients at the Kork Epilepsy Center**

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**Purpose:** The European Reference Network for rare and complex epilepsies EpiCARE reflects the European effort to ameliorate the access to specialized centers and to support clinical studies in order to finally improve the clinical care. Although many patients with rare and complex epilepsy syndromes were always treated at classical epilepsy centers like ours many of these centers including ours are not represented by EpiCARE. We investigated how many of our patients suffer from rare and complex epilepsies according to the Orphanet® register.

**Method:** In this non-interventional observational study all adult in- and out-patients of the Kork Epilepsy Center were assessed during a randomly assigned week (week 40) in 2020. We investigated whether the underlying epilepsy syndrome was listed in the Orphanet® register of rare and complex epilepsies. Children and adolescents as well as long-term residents were not included.

**Results:** In total, 272 patients were collected (mean age 39.3 years, range 18 – 90 years). 128 (47%) fulfilled the Orphanet® criteria for rare and complex epilepsies. Almost all patients showed co-morbidities such as infantile cerebral paresis, hemiparesis, ataxia, intellectual impairment or behavioral disorders. The leading epilepsy syndromes were mesial temporal lobe epilepsy with hippocampal sclerosis (16% of all rare and complex diseases), Dravet syndrome and tuberous sclerosis complex (5% each).

**Conclusion:** Almost 50% of all patients admitted during one week at the Kork Epilepsy Center presented with rare and complex epilepsy syndromes EpiCARE intends to cover.
Long-term prognosis of idiopathic generalized epilepsies (IGE): treatment withdrawal and predictors of seizure control

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Purpose: Idiopathic generalized epilepsies (IGE) are an electroclinical syndrome that include four syndromes according to the latest ILAE 2017 classification. The long-term prognosis of these syndromes and the predictors of seizure control are uncertain due to the scarcity and heterogeneity of the studies. The objective of this study is to analyze the long-term prognosis of these syndromes and describe the predictors of seizure control.

Method: Observational and retrospective study of a cohort of patients diagnosed with IGE between 2008-2020 in a tertiary center. Demographic variables, pharmacological treatment, freedom from seizures and recurrence after withdrawal of treatment were collected.

Results: 101 patients were studied, the majority women (56.4%); with a median evolution of epilepsy of 17 years (interquartile range: 7 – 31). The most frequent syndrome was JME (46.5%). 72.3% were on seizure remission at 1 year; 38.6% at 5 years and 53.3% at 5 years for generalized tonic-clonic seizures (GTCS); but we did not observe significant differences between the different syndromes (p = 0.982). The factors that was significantly associated with no remission of seizures at 5 years was GTCS (OR 4.8; CI 1.2 – 19.1) and polytherapy (OR 8.6; CI 1.9-39.4). Treatment withdrawal was attempted in 27.7%, with a recurrence rate of 71.4%. We did not observe differences in the relapse of seizures between the different syndromes.

Conclusion: JME was the most frequent subtype. We did not observe significant differences in the rates of remission at 1 year and at 5 years. The factors that was associated of seizure persistence was GTCS and polytherapy. The majority of patients with treatment withdrawal relapsed.

Late-onset epilepsy and risk of premature death: the complex role of comorbidities

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Purpose: To identify unique phenotypes and associated risks of death by applying precision medicine machine learning algorithms to a population-based sample of late-onset epilepsy (LOE; aged ≥65 at time of epilepsy diagnosis).

Method: Retrospective cohort study (1998-2019) using linked electronic health, pharmacy, and UK Office of National Statistics data. We applied hierarchical agglomerative clustering to incident cases LOE patients using baseline sociodemographic and clinical features. We used an accelerated time failure model to compare hazards of death and tabulated causes stratified by cluster assignment as the exposure. The primary outcomes were cluster-defining characteristics and the hazard of all-cause death stratified by assigned cluster.

Results: From a population-based sample of incident LOE (n=1048) and 10:1 (n=10,259) matched controls, we identified four unique LOE clusters primarily defined by 1) cardiovascular disease (CVD) and chronic kidney injury (CKI), 2) brain tumors and alcohol misuse, 3) female gender and psychiatric disease, and 4) stroke and dementia. There was high cluster validity, with a multi-class F1 score following stratified 5-fold cross validation of 0.82 (95%CI 0.76-0.88). Epilepsy appeared mild across clusters, with relative defined daily antiseizure medication doses of 0.5 (IQR 0.5-1.0). Despite this, three of four clusters (CVD/CKI, brain tumors/alcohol misuse, and stroke/dementia) were associated with elevated hazards of death compared to matched controls (hazard ratios [HR] 1.48 to 2.03), while the fourth (psychiatric) trended towards significance (HR 1.51; 95%CI 0.97-2.32; p=0.06). Causes of death were commonly defined by CVD and cancer, with few attributed to epilepsy/seizures as either primary or secondary causes.

Conclusion: Unique clusters of people with LOE exist. Despite discrepant comorbid profiles, all have comparably elevated hazards of death compared to controls. LOE appears to exist as a biomarker for severe comorbidities and occult disease, indicating the need for expedient management of concomitant conditions to reduce risk of premature death.
Methods and circumstances of suicide in epilepsy: a population-based study in Sweden

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**Purpose:** In Sweden suicide is 3-4 times more common among people with epilepsy compared to the general population. As part of an epidemiological study of suicide in epilepsy, we here analyze circumstances and methods of suicide.

**Method:** We created a study population including all people living in Sweden in 2006, who were recorded with a diagnosis of epilepsy (ICD G40) in the Swedish Patient Register between 1998 and 2005 (n= 60 952). By linkage to the Cause of Death Register, 226 cases of suicide were identified in the study population, occurring between 2006 and 2011. For these cases, we reviewed all autopsy protocols to validate the cause of death and to collect information on the methods and circumstances surrounding death. We are now reviewing medical records to validate the epilepsy diagnosis.

**Results:** Hitherto, we have reviewed medical records for 133 suicide cases. Most suicides (47%) occurred between ages 45-64 years, while only 18% of suicide cases occurred among people aged ≥65 or older. In the general Swedish population, people aged 65 and older account for 25% of suicides. Poisoning was the most common method (45%) in epilepsy, followed by hanging (21%). In the general population hanging is the most common method (36%). Most suicides in epilepsy occurred in July and more than half of the suicides occurred at home.

**Conclusion:** Our preliminary results indicate that the circumstances of suicide in people with epilepsy differ somewhat from suicide in the general population. In people with epilepsy, the risk for suicide appears to be greatest in young middle age and decrease with age, in contrast to suicide in the general population, where the risk increases with age. Poisoning was the most common method while more violent methods were less common.

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A case-control study developing the Scottish Epilepsy Deaths Study Score (SEDS Score) as a risk prediction model for epilepsy-related deaths

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**Purpose:** To develop a risk prediction model identifying those at high risk of epilepsy-related death.

**Methods:** In this age- and sex-matched case-control study comparing adults (aged ≥16 years) who had epilepsy-related death between 2009-2016 to living adults with epilepsy in Scotland, cases were captured from administrative national datasets linked to mortality records. ICD-10 cause-of-death coding was used to define epilepsy-related death. Controls were recruited from a research database and epilepsy clinics. Medical records were used to capture clinical data. Univariable and multivariable conditional logistic regression was used to develop a risk prediction model consisting of four variables chosen a priori. A sum of the factors present was taken to create a risk index – the Scottish Epilepsy-related Deaths Study Score (SEDS Score). Odds ratios (OR) with 95% CIs were estimated.

**Results:** 224 deceased cases (114 male) were compared to 224 living controls (114 male) – mean age 48 years. In univariable analysis, variables predicting epilepsy-related death were recent epilepsy-related emergency department or hospital admission (OR 5.1, CI 3.2–8.3), living in the two most deprived Scottish areas (OR 2.5, CI 1.6–4.0), developmental epilepsy (OR 3.1, CI 1.7–5.7), alcohol abuse (OR 4.4, CI 2.2–9.2), absent recent neurology review (OR 3.8, CI 2.4–6.1), generalised epilepsy (OR 1.9, CI 1.2–3.0), and mental health problems (OR 1.6, CI 1.0–2.6). The SEDS Score model variables consisted of the first three listed above, alongside the number of comorbidities (adjusting variable). Compared to having a SEDS Score of Zero, those with a SEDS Score of One, Two, and Three, had 3.6x (CI 1.9–6.8), 17.2x (CI 7.4–39.6), and 19.8x (CI 5.1–76.6) increased odds of death, respectively.

**Conclusion:** The SEDS Score may be a helpful tool for identifying adults at high risk of epilepsy-related death and requires external validation.
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Drug-resistant epilepsy in Casablanca-Settat region, Morocco: a cross-sectional study

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Purpose: This study aims to determine the estimated prevalence of drug-resistant epilepsy (DRE) and its related factors, among patients with epilepsy (PWE) in Morocco.

Method: We conducted a cross-sectional study from June to December, 2021 in patients with clinical diagnosis of epilepsy, according to the ILAE definition and with an antiepileptic treatment-duration >12 months, in the Neurology, Neurosurgery and Pediatrics departments, of different sampled hospitals for the Casablanca-Settat region. Sociodemographic and clinical data were collected using a questionnaire during the consultations. Separate and/or combined multi-therapy, a seizure freedom-duration <12 months, patient compliance and adequate posology were the determining factors for classifying DRE. Data were analysed using SPSS software, version 21.0. Statistical significance was set at p <0.05 and logistic regression was performed to determine the associated factors.

Results: In our sample of 174 PWE, main age is 34.57±18.54. The majority had a low-income status (82.2%) and lives in urban areas (74.7%). Illiteracy was in 47.1%. The estimated prevalence of DRE was 27.0%, with pseudo-DRE at 16.1% of which 8.6% were due to poor compliance and 7.5% to inadequate posology. Our analysis shows that early age of the inaugural seizure (p=0.010; OR=0.965), non-medical practices before treatment (p=0.008; OR=2.632), history of febrile seizures (p=0.041; OR=4.571), presence of anxiety-depressive syndrome (p=0.034; OR=1.070), focal to bilateral tonic-clonic seizures (p=0.027; OR=2.262), preictal auras occurrence (p=0.019; OR=2.256), high seizure frequency (yearly seizures) (p=0.000; OR=24.000), abnormal MRI (p=0.011; OR=4.952) and antiepileptic treatment-duration (p=0.029; OR=1.030) are the main significant predictive factors for DRE.

Conclusion: We report that DRE has a non-negligible proportion in our region. Associated factors found can mainly lead to drug-resistance. Adequate antiepileptic prescription and monitoring of good compliance are necessary to avoid misdiagnosis due to pseudo-DRE. Regarding the importance of drug-resistance prevalence, epilepsy surgery may contribute to improve the prognosis of these patients.

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Epilepsy mortality in Wales during COVID-19

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Purpose: The COVID-19 pandemic has increased mortality worldwide and those with chronic conditions may have been disproportionally affected. However, it is unknown whether the pandemic has changed mortality rates for people with epilepsy. We aimed to compare mortality rates in people with epilepsy in Wales during the pandemic with pre-pandemic rates.

Method: We performed a retrospective study using individual-level linked population-scale anonymised electronic health records. We identified deaths in people with epilepsy (DPWE), i.e. those with a diagnosis of epilepsy, and deaths associated with epilepsy (DAE), where epilepsy was recorded as a cause of death on death certificates. We compared death rates in 2020 with average rates in 2015–2019 using Poisson models to calculate death rate ratios.

Results: There were 188 DAE and 628 DPWE in Wales in 2020 (death rates: 7.7/100,000/year and 25.7/100,000/year, respectively. Death rate ratios (2020 compared to 2015–2019) for DAE were 1.34 (95%CI 1.14–1.57, p<0.001) and for DPWE were 1.08 (0.99–1.17, p=0.09). The death rate ratios for non-COVID deaths (deaths without COVID mentioned on death certificates) for DAE were 1.17 (0.99–1.39, p=0.06) and for DPWE were 0.96 (0.87–1.05, p=0.37).

Conclusions: The significant increase in DAE in Wales during 2020 could be explained by the direct effect of COVID-19 infection. Non-COVID-19 deaths have not increased significantly but further work is needed to assess the longer-term impact.
Incidence of febrile seizures post-covid vaccination in children

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Purpose: There is a rising concern among patients with epilepsy and their caregivers about the incidence of breakthrough seizures after COVID-19 vaccination, until now, there is insufficient data in a paediatric population. Describe the incidence of seizures in paediatric patients with epilepsy after COVID-19 vaccination.

Method: Follow-up a cohort of paediatric patients with epilepsy during and after COVID 19 Vaccination and describe if there is a higher incidence of seizures (febrile or not) with COVID Vaccine

Results: 94 paediatric patients, 41 girls and 53 boys were followed between 1 to 5 months after receiving or declining COVID vaccination. 24 patients were refractory, and 70 were seizure-free. 4 patients had a history of febrile seizures. 42 patients refused COVID vaccination due to various causes (most cases related to fear of having seizures related to vaccination)

Fever incidence in our cohort was 4, all of them after second dose
 Patients with controlled epilepsy had Childhood absence epilepsy (1) Panayiotopulos syndrome (1) Jeavons syndrome (1) Dravet syndrome (1), CDH2 (1), Tuberous sclerosis complex (1) Prader Willi syndrome (1) Bainbridge-Ropers syndrome (1) Juvenile myoclonic epilepsy (2) Genetic generalized epilepsies (10). The rest of the patients had focal epilepsies.

The vaccines used in our study were Moderna 4, Pfizer 19 and Sinovac 27.
Only one patient developed a status epilepticus, she has a Malformation of cortical development (MCD), cognitive impaired and PNES. Is not clear whether this status was, in fact, epileptic in nature or was a pseudo status epilepticus, as previously recorded in this patient

Conclusion: There is no evidence of breakthrough seizures related to COVID vaccination in the paediatric population with epilepsy, not even in those with a previous history of febrile seizures.

Needs assessment study to improve care outcomes among neurological-neurosurgical patient population in Western Kenya

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Purpose: Hospital-based studies can help improve patient care outcomes. In Kenya, there is a dearth of such studies among neurological-neurosurgical patient populations. The purpose of the study was to: 1) evaluate the prevalence and demographics of neurological-neurosurgical patients seeking care at Moi Teaching and Referral Hospital (MTRH), and 2) describe the neurology training of Health Care Professionals (HCPs) at MTRH.

Method: A 3-month period prevalence study was conducted at the MTRH inpatient and outpatient settings. Patients were screened daily through daily inquiries, review of admission/medical records and followed up with a patient survey. HCPs were surveyed face to face.

Results: Neurology-neurosurgery patients constituted 6.7% of total inpatients and 0.22% of total outpatients at MTRH during the study period. A total of N=1318(adults n=833, 75% inpatients; pediatrics: n=485; 30.3% inpatients) neurology/ neurosurgery patients sought care. Among the adults, 26.2% were >60 years of age; male: female ratio was 1.56/1; inpatients travelled farther than outpatients (p≤0.0001) with significant coming from rural areas (77.1%; p=0.04). Among the pediatric population, overall, 46.8% were <5 years of age; most inpatients (31.3%) were in the 2-5 years age group, and outpatients (46.4%) in the 5-14 years age group. Most inpatients were from rural areas (43.2%; p<0.0001) and outpatients from peri-urban areas (56.8%; p<0.0001). Most adult outpatients (35.1%) and overall, most children (71.1%) had a diagnosis of epilepsy. Other major adult diagnoses were ischemic and hemorrhagic stroke (22.7%), traumatic brain injury (17.4%). Other major pediatric diagnoses were meningitis (19%), hydrocephalus (16.3%). Of the 266 HCPs who participated in the survey (nurses: 81.6%, physician:10.9%, clinical officers: 7.5%), most (89.5%) reported not receiving any formal neurology training.

Conclusion: Epilepsy was the most common neurological disease. Many other diagnoses reported have the potential to contribute to seizures/ epilepsy. Neurology training/education for HCPs was an important gap identified.
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**Epilepsy monitoring in children in a mixed unit for the last 8 years: characteristics and results**

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**Purpose:** To analyze the characteristics of the pediatric population monitored in the last 8 years in a mixed epilepsy monitoring unit (adults and children) and the results obtained.

**Method:** By reviewing medical records we have collected sex and age, type and etiology of epilepsy, if it can be framed in any epileptic syndrome, family and personal history, treatments tested, complementary examinations performed (neuroimaging, genetic and metabolic tests), and attitude after monitoring.

**Results:** We performed 66 monitoring in 58 patients.
- The age range is from 2 months to 17 years.
- 19 of our patients are female and 39 male.
- 21 of our patients had a family history of epilepsy and 47 neurological comorbidity.
- 26 of the epilepsies are genetic, 19 structural, 5 genetic/structural, 1 metabolic/structural and 9 of unknown etiology.
- 47 are focal and 9 are generalized.
- 15 of the patients can be framed in a specific epileptic syndrome.
- The number of antiepileptic drugs tested ranges from 0 to 11.
- Neuroimaging abnormality is found in 28 patients, abnormal genetic tests in 13 and altered metabolic tests in 1.
- The purposes for monitoring are diagnostic in 32 patients, to establish differential diagnosis in 8, for follow-up in 4 and to make pre-surgical study in 14.
- Subsequent surgery is performed only in two patients and palliative in 1, but changes in therapeutic plan are made in 39 patients.

**Conclusion:** Our sample is heterogeneous.
Epilepsy monitoring in children in our unit is useful in 37 of 49 patients.

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**Estimation of the percentage of the need for antiseizure medications in Ukraine in the conditions of the beginning of the war**

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**Purpose:** On February 24, 2022, the troops of the Russian Federation started a full-scale war in Ukraine. As a result, the provision of patients with antiseizure medication (ASM) has deteriorated significantly and in some regions, where hostilities are most active and which have suffered significantly, has almost stopped. This caused an extremely large deficit in all regions of Ukraine for all ASM.

To determine the amount of care needed for patients with epilepsy, it was necessary to quickly assess the proportion of each ASM among all ones.

**Method:** A survey was conducted over the phone among epileptologists (pediatric and adult) for 2 days with the maximum possible coverage of various regions of Ukraine. Phenobarbital was not analyzed due to the impossibility of importing large quantities to Ukraine.

**Results:** The most commonly used antiepileptic drugs in adults in Ukraine are: Carbamazepine 30%, Valproate 20%, Lamotrigine 15%, Levetiracetam 30%, Topiramate 5%, Oxcarbazepine 5%, the share of other ASMs drugs was less than 1% and was not analyzed.

For pediatric patients – such dates. Carbamazepine 15%, Valproate (all forms) 35%, Lamotrigine (all forms) 13%, Levetiracetam (all forms) 20%, Topiramate 7%, Vigabatrine 3%, Clonazepam 3%, Oxcarbazepine 2%, Clobazam 2%, the share of other ASMs drugs was less than 1% and was not analyzed.

ASM for emergency care (adult and pediatric patients): Benzodiazepines (all drugs, all forms) 70%, Valproate injectable 25%, Levetiracetam injectable 3%, Phenytoin injectable 2%.

**Conclusion:** This survey provided only preliminary and approximate data on the spectrum of ASM prescription in Ukraine, but comparing this analysis with the population of Ukraine and the average prevalence of epilepsy in Europe made it possible to quickly assess the need for ASM humanitarian help for Ukraine in the beginning of the war with Russia even taking into account the inevitable migration processes.
Epilepsy and Reproductive Health

37 Delivery outcomes in women with new-onset epilepsy in pregnancy

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Purpose: Most seizures during pregnancy occur in women who already have epilepsy. Rarely, some women may have their first seizure during pregnancy. In this study, we prospectively investigated delivery outcomes in women with new-onset epilepsy during pregnancy.

Method: 112 pregnant women with epilepsy were prospectively evaluated at the Education – Therapeutic Clinic of the Azerbaijan Medical University, in the neurological and maternity departments of the Clinical Medical Center in Baku over a six-year period. Women were regularly followed by a neurologist and obstetrician till the end of pregnancy. To determine the recurrence of seizures during the pregnancy and after delivery, the women were followed up at least once per three months for a one year period after delivery. Delivery outcomes were compared with those of 277 healthy women in the control group (without epilepsy and without registering chronic diseases).

Results: Of the 112 pregnant women with epilepsy, 12 (10.7%) had their first seizures during the pregnancy: 6 in the 1st, 4 in the 2nd, 2 in the 3rd trimester. The average age at the first seizure was 22.2±4.5 years. The risks of cesarean section and perinatal hypoxia in women with new-onset epilepsy were not increased compared to women with epilepsy before pregnancy (Odds ratio [OR]: 2.64; 95 % confidence interval (CI) 0.54-12.93 and OR 2.18; 95% CI 0.61-7.76, respectively), but were increased in women with new-onset epilepsy compared with controls (Odds ratio [OR]: 13.57; 95% 2.86-64.31 and OR: 3.61; 95 % CI: 1.06-12.27, respectively). None of the women had seizures during labor.

Conclusion: In our cohort, women with new-onset epilepsy may have an increased risk of delivery by cesarean section and perinatal hypoxia compared to pregnant controls. The risks were not increased compared to women with epilepsy before pregnancy but was increased compared with healthy controls.

38 Valproate treatment indication in women with epilepsy who became pregnant

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Purpose: Pre-pregnancy counselling and treatment optimization is essential for women with epilepsy (WWE) planning pregnancy. The aim of this study was to determine whether valproate (VPA) use during pregnancy in women with epilepsy and other conditions was justified, according to current knowledge.

Method: Medical documentation of women using VPA during pregnancies between 1 January 2011 and 31 December 2018 was received from Estonian Health and Welfare Information System Center. Information about diagnoses, treatment decisions, VPA use during preconception period and pregnancy, as well as records of pre-pregnancy counseling, histories of seizure frequency and changes in treatment regimens was analyzed. Factors taken to indicate, that use of VPA during pregnancy was not justified were: 1) focal epilepsy with no attempt to treat the patient with a more appropriate medication; 2)>2-year seizure freedom prior to pregnancy; 3) diagnosis other than epilepsy.

Results: We identified 203 pregnancies in 141 women who became pregnant while using VPA in Estonia during the study period. Most [n = 109 (77%)] of the women had epilepsy diagnoses; generalized epilepsy was most common [n = 66 (61%)], followed by focal [n =22 (20%)] and undetermined [n = 21 (19%)] epilepsy. 19% of the women were treated with VPA during pregnancy due to psychiatric disease. Pre-pregnancy counseling was documented for only 13% (n = 19) of women who subsequently became pregnant while using VPA. According to chosen criteria VPA treatment was justified in only 33 (23%) cases. In 12 (9%) cases, the available information was insufficient to determine whether this treatment was justified, and in 96 (68%) cases it would have been possible to try to avoid VPA use during conception and pregnancy.

Conclusion: Awareness of the need for pre-pregnancy counseling and treatment optimization in WWE should be increased among medical specialists.
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Women with epilepsy have worse pregnancy, delivery and perinatal outcomes than women without epilepsy: a systematic review and meta-analysis

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Purpose: To investigate pregnancy, delivery and perinatal outcomes of women with epilepsy (WWE) compared to women without epilepsy (WWoE).

Methods: MEDLINE, EMBASE, CINAHL, and PsycINFO searches using standardised systematic review methodology, with no language or date restrictions, identified observational studies comparing WWE and WWoE. Study quality and risk of bias were assessed using the Newcastle-Ottawa Scale. Unadjusted odds ratios (OR) or mean differences (MD) with 95% confidence intervals (CI) are reported for the 27 statistically significant outcomes from 36 investigated. The I² statistic determined statistical heterogeneity and random (I² >50%) or fixed (I² <50%) effects models.

Results: Of 7,757 articles identified, 74 were included for meta-analyses. WWE had increased odds of miscarriage [OR 1.78 (95%CI 1.16-2.75), I²=65%], preeclampsia [1.44 (1.30-1.60), I²=50%], antepartum haemorrhage [1.38 (1.32-1.45), I²=0%], placental abruption [1.51 (1.20-1.90), I²=43%], gestational diabetes [1.21 (1.00-1.46), I²=57%], fetal distress [1.05 (1.03-1.08), I²=0%], bleeding during pregnancy [1.18 (1.05-1.34), I²=46%], and intrauterine growth restriction [1.79 (1.72-1.86), I²=81%]. WWE had increased odds of stillbirth [1.37 (1.27-1.47), I²=36%], induced labour [1.41 (1.25-1.60), I²=83%], premature rupture of membranes [1.19 (0.95-1.49), I²=80%], assisted (forceps/vacuum) delivery [1.13 (1.02-1.26), I²=75%], caesarean section [1.50 (1.39-1.62), I²=82%], preterm birth [1.32 (1.18-1.47), I²=52%], and any pregnancy loss [1.40 (1.30-1.50), I²=31%]. Neonates born to WWE had increased odds of small for gestational age [1.40 (1.25-1.57), I²=56%], birthweight<2500 grams [1.35 (1.18-1.54), I²=53%], 5-minute Apgar<8 [1.28 (1.01-1.63), I²=60%], congenital anomalies [1.69 (1.45-1.98), I²=79%], neonatal intensive care unit admission [1.88 (1.45-2.42), I²=74%], neonatal/infant death [1.86 (1.55-2.55), I²=37%], reduced body length [MD=-0.31 (0.56, -0.06), I²=75%], birth weight [-87.89 (-85.29, -0.49), I²=39%], and 5-minute Apgar <0.16 (-0.26, -0.05), I²=63%]. WWE had increased odds of maternal death during or shortly after pregnancy [11.24 (8.66-14.59) I²=41%].

Conclusions: WWE have significantly worse pregnancy, delivery and perinatal outcomes compared to WWoE. These require consideration during pregnancy counselling.

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An audit on women with epilepsy and the national epilepsy in pregnancy guideline

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Epilepsy is the most common neurological disorder affecting pregnancy. In 2020, MBRRACE reported a significant increase in maternal mortality and SUIDEP in WWE. One key recommendation was that pregnant WWE are ensured access to specialist epilepsy care. This audit aimed to assess adherence to National Guidelines for WWE attending general antenatal clinics prior to the introduction of a specialist antenatal clinic for WWE.

The audit was carried out in a tertiary maternity hospital, Dublin, Ireland. Medical records between January-December 2020 were analyzed and compared to the standard of care recommended in the National Guidelines for management of Epilepsy in Pregnancy (HSE/2014). Documentation of demographics, epilepsy type, antiepileptic drugs (AEDs), AED levels, interaction with epilepsy specialists and presence of care-plans was assessed. Mode of delivery, APGARs, fetal anomalies and breastfeeding information were also recorded.

A total of 78 women had a history of seizures in their antenatal booking summary. 21 patients were excluded from the audit due to lack of information in the chart and no clear diagnosis of epilepsy. Of the 57 WWE included in the audit, 45.6% and 42.1% were diagnosed with Convulsive Seizures or Non-Convulsive seizures respectively whether part of a partial or generalized onset disorder. 21% of patients had a documented seizure during their pregnancy.

42.1% of patients had interactions with an epilepsy specialist during their pregnancy. Only 47.4% had documentation of taking the recommended 5mg Folic acid antenatally. 1.8% had prenatal AED levels documented and 21% had AED levels documented during the pregnancy. The majority had no labour or postnatal care plan devised.

This audit showed shortcomings in recommended standards of care for WWE in pregnancy. A dedicated antenatal clinic for WWE, which aims to streamline communication between medical specialties, patients and care providers while improving outcomes for WWE is due to commence Q1 2022.
Pregnant women with epilepsy: three decades of neurological experience

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**Purpose:** Pregnant women with epilepsy (PWWE) is a special group among patients living with epilepsy. Our aim was to study the characteristics, treatment and outcome of pregnancies among PWWE in the East-Hungarian region.

**Method:** Retrospective analysis of PWWE in the Epilepsy Database (University of Debrecen, Department of Neurology, Outpatient Epilepsy Ward) between 1992 and 2020. Three groups (GI-GIII) were formed based on the time period of pregnancy between 1992-2001, 2002-2011 and 2012-2020, respectively. Introduction and widespread use of safer antiseizure drugs (ASD) during pregnancy served as milestones.

**Results:** There were 51, 61 and 72 pregnancies in GI, GII and GIII, respectively. Altogether, 22.5% of patients had a positive family history for epilepsy. For the outcome of pregnancies, the 'riskiest' type (generalized) was the most frequent (61%). Altogether, 12.8% ended in spontaneous abortion. Comparing the three groups, the probability of abortion was higher in the first two groups, OR:2.4 [1.4;3.4] p<0.0001. The majority of patients (85%) remained seizure free during pregnancy. Due to familial predisposition, major malformations were detected in two foetuses. The proportion of live births was significantly higher in 2012-2020 (p=0.008). ASD was withdrawn in 33% of patients in GI and GII during foetal organogenesis. Most patients were on monotherapy (67%) in all groups. Patients were prepared in time and medication was switched to the actual safest ASD if possible, so GI, GII and GIII dominantly received carbamazepine, carbamazepine and lamotrigine, levetiracetam and lamotrigine, respectively. Based on serum levels and EEG findings, doses were elevated in trimester 2, if necessary. Of those not having regular check-ups (15%), 12 took valproate, starting from childhood. They presented in trimester 2 or 3.

**Conclusion:** Since the introduction of newer type ASds, the number of pregnancies and births has been increasing. Our data suggest that regular epileptological care for PWWE is highly important.

The rate of and factors associated with delivery by cesarean section among women with epilepsy: time trend in a single-centre cohort

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**Purpose:** Caesarean section (CS) rate in women with epilepsy (WWE) in the literature is relatively high. The reason for this is unclear. Since there is a gap of knowledge on this issue in Poland, we aimed to determine the rate of CS among WWE in an epilepsy centre in Poland, assess factors increasing the likelihood of CS, and analyze indications for CS.

**Method:** Clinical data were collected in a longitudinal prospective database of WWE in a single center in Poland between 2000-2019. To calculate CS rates as a comparator, we used the number of deliveries in Mazovian hospitals obtained from the National Health Fund. Correlations between year and the CS rate and indications and the year were investigated by a linear regression model. One-way mixed models were used to identify the factors influencing the likelihood of CS in WWE.

**Results:** The analysis included 1021 deliveries in 864 pregnant WWE. The mean rate of CS in WWE was 49%. This rate increased from 18.92% to 57.58% over the 20 years, with a linear increase of 1.893% annually. In the general population of Mazovia, the CS rate increased from 18.95% to 41.71%, with a linear increase of 1.289% annually. The most important factors increasing the odds of CS in WWE were the presence of generalized seizures in the third trimester (OR 4.421) and twin pregnancy (OR 4.108). The most frequent indication type for CS was obstetric (58.1%), followed by epilepsy-related (25.2%) and other indications (21.9%). Almost half of those with epilepsy as the sole indication for CS had no seizures during pregnancy, and nearly 70% did not have generalized seizures.

**Conclusions:** These results suggest that epilepsy-related indications for CS in WWE are overused and that more careful pregnancy monitoring, treatment optimization, and well-defined indications for CS are needed for WWE.
Epilepsy in Older People

23 Late-Onset seizures; Stroke Treatment and life-style Intervention Trial (LOSTIT)

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Purpose: A first seizure after middle age can be a warning sign of stroke, presumably because of occult cerebrovascular disease. Using Swedish registers, we found that 5–20% of first-seizure patients age >50 will suffer stroke within ten years (Zelano et al., 2017). Late-onset seizures doubles the risk of ischemic and triples that of hemorrhagic stroke (Larsson et al., 2020). Guidelines increasingly mention vascular workup, but do not provide advice on management. Statins are epidemiologically associated with lower epilepsy risk (Etminan et al., 2010), but whether they reduce the risk of epilepsy after a first late seizure is not known. Against this background, we developed a protocol for a randomized open-label trial: Late-Onset seizures: Stroke Treatment and lifestyle Intervention Trial (LOSTIT).

Method: The protocol was developed by stroke and epilepsy experts. LOSTIT will assess the effect of risk factor intervention after a first late seizure (age >50) on stroke risk (primary outcome), or death/stroke severity/epilepsy (secondary outcomes).

Results: LOSTIT will randomize patients between a) standard care and b) treatment according to current European guidelines for primary prevention in individuals with high vascular risk: statin, BP target of at least 140/90, and lifestyle advice. Follow-up will be register-based for outcomes to minimize drop-out. Clinical follow-up is performed for safety. Sample size calculations based on an estimated effect size of 30% indicate a need for 1356 patients per group in an end-point-driven study.

Conclusion: Obtaining randomized evidence for cardiovascular prevention after a late-onset seizures will be challenging. A vanguard/pilot phase evaluating feasibility would be preferable. The number of patients required is larger and follow-up needs to be longer than in many epilepsy trials, so LOSTIT may require multinational collaboration. On the other hand, the low-risk intervention and potential benefit could well motivate the effort.

244 New-onset seizures in elderly: classification, risk factors, etiology and its impact on quality of life and caregiver burden

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Purpose: Incidence of seizures in elderly is highest and management is challenging in view of atypical presentation and co-morbidities. The aims of this analysis were to study classification, etiology and risk factors in new onset seizures in elderly (more than 60 years) and its impact on quality of life (QOL) and caregiver burden.

Method: All elderly presenting with new-onset seizures and subjects with history of seizure with onset after the age of 60 years were included. QOL and caregiver burden was assessed after 8 weeks of inclusion in the study. QOL was assessed with WHO-QOL-old and compared with age matched controls. Caregiver burden was assessed with Zarit Burden questionnaire.

Result: 80 subjects fulfilling inclusion criteria and 80 age matched controls were recruited between July 2020 to December 2021. There was no difference of age (68.30±6.22 vs 69.09±6.07; p=0.39) and gender (M: F= 50:30 vs 48:32; p=0.74). 58 (72.5%) cases had generalized seizure followed by focal in 20 (25%) and unclassified in only 2 (2.5%). Hypertension was the commonest risk factor seen in 49 (61.3%) followed by ethanol intake in 32 (40%) and diabetes in 31 (38.8%). Cerebro-vascular disease was the commonest etiology [30(37.5%)] followed by infection (15%). 13 (16.2%) subjects died during hospital stay, 19 (23.7%) died after discharge from hospital and QOL and caregiver burden was assessed in remaining 48 (60%). The scores of three domains of WHO-QOL-old – Autonomy, Past, present and future activities and Death and Dying concerns were significantly low in cases. 62.5% care-giver reported mild to moderate burden.

Conclusion: Generalized seizure is the commonest seizure type in late onset seizures. Hypertension is the commonest risk factor and cerebro-vascular diseases is the commonest etiology. Late onset seizures affect some components of QOL and is mild to moderate burden to a large number of caregivers.
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Poststroke seizures: do reperfusion therapies play a role?

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Purpose: Seizures are among the most important complications of ischemic stroke. New treatment modalities, such as systemic intravenous thrombolysis or endovascular mechanical thrombectomy can achieve reperfusion of large ischemic tissue. However, some studies suggested that reperfusion therapies can increase the risk of poststroke seizures. So we aimed to investigate the relationship between reperfusion therapies and development of poststroke seizures in patients with ischemic stroke.

Method: The study was performed retrospectively by evaluating the medical records of the patients with a diagnosis of ischemic stroke. Reperfusion therapies were determined as intravenous thrombolysis and mechanical thrombectomy. Patients with poststroke seizures were identified. Poststroke seizures were classified as early-onset seizures and late-onset seizures. Early-onset seizures were defined as seizures that occurred within fourteen days following the ischemic stroke and late-onset seizures were defined as seizures that developed after the fourteen days.

Results: A total of 1033 patients with ischemic stroke were identified, of which 73 (7.1%) had seizures. Two hundred and twenty-one (21.3%) patients received intravenous thrombolysis and 153 (14.8%) patients underwent mechanical thrombectomy. Poststroke seizures were reported in 22 (14.3%) patients who received mechanical thrombectomy (p=0.01). Fifty (68.4%) patients presented early-onset seizures and 23 (31.5%) patients developed late-onset seizures. Early-onset seizures were reported in 18 (36%) patients among the patients who received intravenous thrombolysis (p=0.02). Late-onset seizures were defined in 10 (43.5%) patients who had mechanical thrombectomy (p=0.03).

Conclusion: We demonstrated that performing mechanical thrombectomy can increase the occurrence of poststroke seizures. Also, treatment with intravenous thrombolysis can increase the risk of early-onset seizures, whereas receiving mechanical thrombectomy can increase the risk of late-onset seizures. Many studies have shown the superiority of reperfusion therapies including intravenous thrombolysis and/or mechanical thrombectomy over standard treatments for patients with ischemic stroke. But we should be aware that reperfusion therapies can increase the risk of developing poststroke seizures.

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Late-onset temporal lobe epilepsy of unknown etiology: neuropsychological profile, cerebrospinal fluid biomarkers, and connectivity EEG characteristics

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Background: Temporal lobe epilepsy of unknown etiology (TLE) is one of the most frequent types of focal epilepsy in older adults. In this context, two main groups can be identified: patients who have a long history of TLE (long-lasting TLE, LLTLE), and those who develop epilepsy de novo in later life (late-onset epilepsy TLE, LOTLE). Despite the bulk of the literature focused on dementia as a startling cause of epilepsy in the elderly as well as on cognitive performance in young-onset epilepsy, little is known on cognition among people with LOTLE. This study aims to investigate the neuropsychological profile, the cerebrospinal fluid (CSF) neurodegenerative biomarkers, and the resting-state EEG connectivity characteristics in LOTLE patients.

Methods: Twenty-five patients with LOTLE and 25 sex-, age- and seizure frequency-matched patients with LLTLE were enrolled. Patients underwent extensive neuropsychological evaluation, CSF neurodegenerative biomarkers assessment (Aβ42, phospho-tau, and total tau classified through A/T/(N) system), and 64-channels resting-state EEG. EEG signals were sectioned into 2-s epochs. Coherence, as measured by weighted phase-lag-index (PLI), weighted PLI (wPLI), and imaginary part of the Coherence, was employed for the functional connectivity (FC) analysis. Connectivity matrices for each epoch for each FC function were built and then averaged across epochs to get subject-level connectivity matrices.

Results: Compared to the LLTLE-group, LOTLE-group showed more impaired working memory, language, and attentive functions. CSF neurodegenerative biomarkers were normal in all patients except for three subjects (1.A+, 2.A+, 3.T+). In the LOTLE-group, FC analysis showed increased whole-brain connectivity in the alpha-band, with significantly higher connectivity in the frontoparietal regions.

Conclusion: Patients with LOTLE present a distinctive neuropsychological and FC profile. Our results highlight a possible neurodegenerative process underlying LOTLE onset. Future longitudinal studies will be necessary to characterize the underlying pathophysiological basis of the cognitive deficits and to assess the progression extent.
Epilepsy in Resource-restricted Settings

103 Epilepsy management in sub-Saharan Africa and teleneurology. Tracking the Intersectoral Global Action Plan 2022-2031

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Purpose: The Intersectoral Global Action Plan (IGAP) 2022-2031 aims to increase access to epilepsy care in developing countries mainly at primary care level. In Sub-Saharan Africa (SSA) 2/3 of people with epilepsy (PWE) have no access to treatments; there is 1 neurologist every 2 millions inhabitants; more than 90% of PWE are managed by health care providers (HCP) whose education in neurology is insufficient. In SSA there are more than 26 millions of HIV+ people and HIV is a risk factor for epilepsy. IGAP calls to better integrate epilepsy and HIV. Teleneurology brings neurologists where there are none: to work properly it requires a certain education in neurology. We report on the impact of education and training to local HCP on teleneurology requests from primary care HIV-centres in SSA.

Method: Global Health Telemedicine (GHT) offers free teleneurology service to developing countries. Voluntary European neurologists send their advices from remote to SSA HCP of the Disease Relief through Excellent and Advanced Means (DREAM) health program operating in 10 SSA countries. In Malawi and Central African Republic (CAR) DREAM follows 18770 patients: 81% are HIV+, 588 (3.1%) suffer from epilepsy. The Italian Society of Neurology, the C.Besta Neurologic Institute and the Mariani Foundation joined the DREAM-GHT epilepsy program in Malawi and CAR. In 2021 two video-electroencephalograms were installed and 6 face-to-face education and training courses have been delivered to local HCP: 4 in Malawi, 2 in CAR. Several sessions from remote were also offered. In addition to basic knowledge in neurology and epilepsy, integration with HIV was part of the education and training program.

Results: In 2021 teleneurology consultations were 802 compared to 141 in 2020; >90% were for PWE.

Conclusions: Education and training to local SSA HCP improves teleneurology. Developing IGAP in SSA requires enhanced and tailored education programs on epilepsy.
Nodding Syndrome Alliance - preliminary data on clinical management from a multi-sectoral initiative addressing nodding syndrome and other forms of epilepsy in Western Equatoria, South Sudan

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Purpose: Nodding Syndrome (NS) is a degenerative neurological condition and form of epilepsy. Western Equatoria (South Sudan) presents high prevalence of NS and Other Forms of Epilepsy (OFE), from 2.3% in Lui to 5% in Mwolo. The age of NS onset ranges between 5 and 15 years old, complications may result in early death, due to social exclusion caused by stigma and lack of treatment. The initiative funded by Italian Agency for Development Cooperation intends to show that NS and OFE can be stabilized by regularly administering standard antiepileptic drugs, which are rarely available or affordable to such neglected patients.

Method: The 3-year comprehensive intervention aims at increasing community resilience towards NS/OFE through identification, referral, and treatment as well as socio-economic inclusion of people with NS/OFE. The project funds 3 epilepsy clinics (Mundri PHCC, Maridi Hospital, Lui Hospital), treating NS/OFE and complications. By December 2021, 19 months since inception, the clinics had enrolled and followed up 3170 patients. Data extracted from the clinics’ registers and databases were analyzed in MS Excel.

Results: Patients’ median age is 21, 1807 (57%) in the 15-24 age group. The 51.1% of patients (1631) are male. Concerning treatment, 1641 (51.8%) receive Carbamazepine, 835 (26.3%) Phenobarbital, 444 (14%) Phenytoin, 246 (7.8%) Valproic Acid. On average, 93.9% of patients adhere to treatment, 94.2% reported a decrease in seizures. The quality of life was perceived as “Better” and “Much better” by 49.8% and 39.6% of patients, respectively. 555 patients (17.5%) were recorded as probable or confirmed NS, while the majority (1488, 46.9%) with both NS and OFE. Accurate diagnosis remains challenging.

Conclusion: Relevance and feasibility of promoting access to treatment for NS/OFE is confirmed. Further analyzes shall target community networks’ contribution to demand for and adherence to treatment, rational use of drugs, patients’ provenance and clinical characteristics.

The impact of the COVID-19 pandemic on people with epilepsy living in Rwanda

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Purpose: Understanding the impact of the COVID-19 pandemic on persons living with epilepsy (PwE) is important, especially in Rwanda in view of the 4.9% high prevalence of epilepsy. In low-resource settings sustainable access to antiseizure medication is limited, especially during lockdown. Moreover, social isolation and imposed changes in daily routine might induce stress, increasing seizure frequency. We measured the impact of the COVID-19 pandemic on access to care, psychological well-being and seizure frequency of persons living with epilepsy in Rwanda.

Method: We conducted a cross-sectional study with a study population consisting of PwE enrolled between February-December 2018 and between December 2020-January 2021 at the tertiary CARAES neuropsychiatric hospital (Kigali). Experienced researchers administered a telephone SARS-CoV-2 survey, including QOLIE-10 questions and a Kinyarwanda validated PHQ-9 questionnaire.

Results: A total of 102 patients (47 female; mean age 34 years) were included. Before lockdown, 73 PwE were seizure-free. Seizure frequency did not change significantly during lockdown (p=0.388), with only four patients reporting a seizure increase. Quality-of-life during lockdown was rated ‘not good to very bad’ in 24.8% of PwE, 47.5% felt downhearted and 91.1% were afraid of seizures. Depression was diagnosed in 15.7%, as opposed to 5.7% before lockdown. Only one patient with depression reported increased seizure frequency after having been seizure-free before lockdown. Five patients with depression reported more intense seizures during lockdown with similar seizure frequency. Shortage of anti-seizure medication at home during lockdown was reported by six PwE; one reported increased seizure frequency. Medication type was changed in another six patients with one reporting increased seizure frequency after having been seizure-free before lockdown and one reporting more intense seizures during lockdown with similar seizure frequency.

Conclusion: Despite lockdown, access to care for PwE in Rwanda was maintained with limited impact of lockdown on seizure frequency, although psychological well-being was affected.
Social determinants that may influence Moroccans’ understanding and perceptions towards epilepsy

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Sociocultural beliefs about epilepsy impede medical treatment and social acceptance of people with epilepsy. These barriers can lead to disability and contribute to the stigmatization of people with epilepsy. In this study, we raised the determinants that may influence understanding and perceptions about epilepsy. We conducted a cross-sectional study in which data were collected from a sample of 385 individuals in the Sous Massa region of southern Morocco via a questionnaire. The results of the analysis of the collected questionnaires were processed using IBM SPSS Statistics 20.

According to the results of the study, 16% of the participants believe that epilepsy is a psychiatric disorder and 14% believe that it is synonymous with “madness”. Also, bewitchment and possession (Jinn) were among the causes raised by, respectively, 13% and 15% of participants. As for treatment, 17% suggested spiritual therapies. Furthermore, about a quarter of the participants admit that medical care and treatment allow people with epilepsy to lead a normal social and professional life. In addition, there was a statistically significant association (p =0.000, < 0.05) between a lower education level, older age, rural origin, compared to a wrong understanding of epilepsy. Also, there was a statistically significant association (p =0.000, < 0.05) between a lower education level, rural origin, compared to a choice of negative perceptions towards people with epilepsy.

Therefore, people with epilepsy face the consequences of sociocultural misconception and stigma. Hence, the implementation of public awareness programs about epilepsy in urban and rural areas is necessary.

Epidemiology of true drug resistant epilepsy in an epilepsy clinic related to tertiary referral hospital

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Purpose: Most patients with epilepsy achieve seizure freedom with anti-seizure medications (ASMs), however 20-40% of patients are resistant to medication. We aimed to determine the prevalence of uncontrolled seizures, the underlying causes and their predictive value in tertiary referring hospital.

Method: A hospital-based cross-sectional study, conducted over two stages. A preliminary stage to identify the point prevalence of uncontrolled seizures and a second stage that compared the clinical, neurophysiological and radiological aspects of a sample of patients with uncontrolled seizures to patients with controlled epilepsy. Stepwise logistic regression was performed to detect possible predictors for true drug resistant epilepsy (DRE).

Results: The point prevalence of uncontrolled epilepsy was 58.3%, among them 24.2% were true DRE. In the studied sample of uncontrolled patients (n= 194), 70 (36.1%) patients were true DRE while 124 (63.9%) patients were uncontrolled due to non-adherence to medications. Significant higher percent of patients with true DRE showed positive consanguinity (p=0.002), abnormal neurological examination (p=0.027), inter-ictal epileptic discharges (p =0.03) and underlying structural lesions (p=0.011) when compared to controls. The identified predictors for true DRE were younger age of onset (OR: 0.563), presence of neurological deficit (OR: 5.291) and use of ≥3 ASMs (OR: 1.945).

Conclusion: The percent of uncontrolled epilepsy in our tertiary care hospital is comparable to the previous reports, with non-adherence being the major cause for pseudo-intractability. A set of variables that may act as predictors for true DRE, which when considered along with causes of non-adherence will aid in better management of patients with epilepsy.
Challenges and solutions for epilepsy surgery in developing regions of sub-Saharan Africa and a proposal to reduce them

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**Purpose:** To reduce disparities in access to epilepsy surgery (ES) between high income and low income countries. This work aims to serve as a global call for partnership to centers of excellence in ES of Europe, America, Asia and Australia for collaboration in order to establish program for ES in Cameroon and other resource limited regions.

**Method:** A review was performed to assess the current status of ES in LMIC as a starting point for future initiatives in low- and middle-income countries. The current body of literature on ES in LMIC was conducted through the United States National Library of Medicine Pubmed search engine. Search terms included “Epilepsy surgery”, “developing countries,” “low and middle income”, and other related terms.

**Results:** It was found that about five billion people lack access to safe surgical care, the burden of disease amenable to treatment with ES remain unknown. Although many successful, long-term, international surgical collaborations are published, reports in the sub-field of ES are lacking.

**Conclusion:** Awareness of global surgical disparities has increased dramatically while global guidelines for ES are currently lacking. Partnerships between centers in LMIC and HIC are making progress to better understand the burden of disease in LMIC and to create context-specific solutions for practice in the LMIC setting, the collaboration between center of excellence in ES and initiatives aiming at establishing ES in resource-limited regions could be meaningful strategical steps to be initiated for the wider practice of ES. Experience gained from similar collaborations is urgently needed.

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Role of resective surgery in the patients over 60 years old with drug-resistant epilepsy

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**Purpose:** Epilepsy surgery in elderly population has been controversial. The concern for patients with long-lasting epilepsy as well as higher surgical risk has often rendered this group of patients as non-candidates for surgery despite possible benefits. Our objective was to analyze the role of resective surgery in patients over 60 years, assessing outcomes and safety.

**Methods:** We conducted a retrospective analysis of 595 patients who underwent resective epilepsy surgery at our center from 1999-2019 (20 years). Thirty-one patients who were 60 years of age or older were identified. Sixty patients of 59 years of age or younger were randomly selected as control group. Population characteristics, presurgical evaluations, postoperative outcome and complications were analyzed.

**Results:** No significant differences were found between both groups in terms of hemisphere dominance, side of surgery, lesional/non-lesional ratio and incidence of TLE over extratemporal epilepsy. Median age (p<0.0001), duration of epilepsy (p=0.0192), and the need for invasive recording in younger patients (p=0.0298) were statistically significant (Tables 1 and 2). Engel I at 6 months, 1 year and 2 years were 89.7%, 96.2% and 94.7% for the older group and 75% (p=0.159), 67.3% (p=0.004) and 75.8% (p=0.130) for the younger group, respectively. The subgroup of TLE exhibited better seizure outcomes in both groups but was higher for the older group. Neurological complication rates did not differ significantly between groups, however medical and other minor complications occurred more frequently in the older group.

**Conclusion:** Epilepsy surgery in patients over age 60 had an equal or better outcome at one year than in younger patients. A trend towards more lesional temporal lobe epilepsy cases was found in the older group. Although peri-operative risk might be higher, good results can be obtained and the decision to operate should be individualized on patient’s inherent risk and not due to age.
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Development of epilepsy surgery in Armenia

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Purpose: To present our experience in the development of epilepsy surgery in Armenia by mandatory pre-surgical work-up (32-channel video-EEG and 1.5 or 3 Tesla MRI with epilepsy protocol) done by motivated doctors with the help of foreign colleagues.

Method: From 2016 to 2021 twenty six patients (14 males) aged 4-37 years (mean-17.3) were operated at “Arabkir” Medical Center, Armenia. Duration of epilepsy was 1-35 years (mean-13).

Febrile seizures were reported in 10 patients (38%) and co-morbidities were present in 6 (23%): 3 (11.5%) - intellectual disability, 2 (5.2%) - learning disability, and 1 (2.6%) - autism. All patients underwent long-term video-EEG monitoring and MRI with epilepsy protocol. In 23 (88.4%) we obtained ictal EEG. In 13 (50%) PET scan was done (“Institute of Human Brain” in St. Petersburg). All patients had pre-surgical neuropsychological testing. Etiology of epilepsy was hippocampal sclerosis in 11 (42.3%), tumor in 6 patients (23%), focal cortical dysplasia in 6 (23%), and residual brain damage - in 3 (11.5%). Follow-up period was 2 months – 5 years (mean 2.2 years). Cases were discussed in video-call conferences and patients eligible for surgery were selected. Team of epilepsy specialist, surgeons and anesthesiologist travelled once a year to perform surgeries on site.

Results: In 11 (42.3%) anterior temporal lobectomy was done; 6 (23%) had tumor resection; 6 (23%) -lesionectomy for FCD, and 3 (11.5%) - hemispherotomy. Surgery outcome was assessed by Engel Outcome Scale. Seventeen patients (65.3%) had IA, 3 (11.5%) - IB, 2 (7.7%) - ID, 2 (7.7%) - IIB, and 2 (7.7%) - IVB outcome. Therapy was discontinued in 11 cases (42.3%). For the first time in Armenia awake craniotomy, intra-operative neuromonitoring, Wada test and hemispherotomy were performed.

Conclusion: We believe that our experience can serve as a model to develop epilepsy surgery in countries with limited resources.

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Surgical treatment of neocortical non-convulsive status epilepticus

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Purpose: Non-convulsive status epilepticus (NCSE) is a challenging neurological emergency requiring prompt diagnosis and treatment. Pharmacotherapy is the first-line treatment for those patients, and only a few cases of NCSE who underwent surgical treatment have been reported.

Method: Two patients diagnosed as NCSE in accordance with the modified Salzburg’s criteria were investigated. Case 1 was a 65-year-old right-handed male, showing decreased ADL, cognitive impairment and disinhibited behavior a few days after brief generalized convulsive seizure. He had been diagnosed as post-traumatic epilepsy for the last two years, and already taking multiple AEDs. MMSE scored 13/30. EEG showed frequent periodic epileptiform discharges (EDs) at the right fronto-central area. Case 2 was a 65-year-old right-handed male, who showed progressive decline of ADL, cognitive impairment and hemispatial neglect, after the treatment of convulsive status epilepticus due to the resection of metastatic brain tumor 6 months before. He was already taking multiple AEDs. MMSE was 22. EEG showed frequent periodic EDs at the right parietal area, adjacent to the area of resected tumor. Because both were refractory to multiple AEDs, surgical intervention was planned after obtaining written informed consent.

Results:

Case 1 underwent focus resection of seizure onset zone at the inferior parietal area and multiple subpial transection of irritative zone at the middle frontal gyrus after invasive monitoring. Postoperatively, MMSE improved to 17 without any additional deficits. Residual focal aware seizures were seen once a month. His paroxysmal psychiatric abnormal behaviors also subsided.

Case2 underwent resection of posterior parietal area showing the most frequent EDs and MST of surrounding parietal cortices under ECoG. Postoperatively, he was free of seizures and MMSE improved to 29. He was discharged home with independent ADL.

Conclusion: Surgical treatment of neocortical focus resection could be recommended for a selected patient with drug-resistant NCSE.
Semi-invasive presurgical video-EEG-monitoring with epidural foramen ovale and peg electrodes – a 25-year perspective

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Objective: To assess the diagnostic significance of semi-invasive (SI) presurgical video-EEG-monitoring (VEM) utilizing epidural foramen ovale (FO) and peg electrodes.

Methods: We retrospectively analyzed clinical, electrophysiological, and imaging characteristics of 180 consecutive patients that underwent SI VEM between 1996 and 2021. We compared per patient the ratio of seizures with ictal onset, i.e., definite seizure onset on one side and/or in one region, to the total number of seizures recorded, each during scalp and SI VEM. Multivariate logistic regression was used to assess predictors of clinical and electrophysiological outcomes.

Results: SI VEM allowed for immediate resection recommendation in 36 patients (20.0%) and excluded this option in 85 (47.2%). In 59 patients, additional invasive investigations (51 patients unilateral subdural, 8 bilateral depth) were needed. Eventually, resection was recommended in 72 patients (40.0%). During SI VEM, a clear ictal onset was identified in 137 patients, compared to 96 during scalp VEM, p= .004. Clear ictal onset ratio increased from 0.53±0.42 on scalp to 0.71±0.39 on SI VEM, p< .001. Following multivariate analysis, predictors for SI VEM determination of clear ictal onset were temporal lobe epilepsy (OR 2.9, p= .03) and lesional imaging (OR 3.1, p= .01). Predictors of surgery recommendation were temporal lobe epilepsy (OR 6.8, p< .001), FO seizure onset (OR 6.1, p= .002), and unilateral interictal epileptic activity on SI VEM (OR 3.8, p= .02). Among 60 patients with 1-year postsurgical follow-up, 53.3% were seizure-free (27/51 temporal and 5/9 extratemporal resection). Postsurgical seizure freedom was predicted by FO ictal onset (OR 5.8,p= .01). Two patients experienced intracerebral bleeding and 42 patients had minor complications.

Significance: SI VEM, in selected patients, adds clinically significant electrophysiological information and allows for clinical decision making in the majority of cases without exposing patients to the risks of invasive procedures.

Protocol for multicenter comparison of interictal high frequency oscillations as a predictor of seizure freedom

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Purpose: In drug-resistant focal ictal, interictal high frequency oscillations (HFO) recorded from intracranial EEG (iEEG) may provide clinical information for delineating epileptogenic brain tissue. The iEEG electrode contacts that contain HFO are hypothesized to delineate the epileptogenic zone; their resection should then lead to postsurgical seizure freedom.

Method: We test whether our prospective definition of clinically relevant HFO is in agreement with postsurgical seizure outcome. The algorithm is fully automated and is applied to all datasets. The aim is to assess the reliability of the proposed detector and analysis approach. We use automated data-independent prospective definition of clinically relevant HFO that has been validated in data from two independent epilepsy centers. In this study, we combine retrospectively collected datasets from 9 independent epilepsy centers. The analysis is blinded to clinical outcome. We use iEEG recordings during NREM sleep. We automatically detect HFO in the ripple and the fast ripple band. The HFO that we consider clinically relevant is defined as the simultaneous fast-ripple and ripple. We calculate the temporal consistency of each patient’s HFO rates over several data epochs. Patients with temporal consistency <50% are excluded from further analysis. We determine whether all electrode contacts with high HFO rate are included in the resection volume and whether seizure freedom was achieved at ≥2 years follow-up. We estimate the 95% confidence intervals for the confusion matrix of the HFO classification.

Results: The lower limit for the number of patients that must be included before publication is N = 255. The expected 95% confidence interval for the expected cohort size are above chance level.

Conclusion: Applying a previously validated algorithm to a large cohort from several independent epilepsy centers may advance the clinical relevance and the generalizability of HFO analysis as essential next step for use of HFO in clinical practice.
Responsive neurostimulation (RNS) is used off-label for seizure management in pediatric patients with drug-resistant focal, multifocal, and generalized epilepsy. Our study aims to determine the safety and efficacy of RNS in pediatric patients with focal, multifocal, and generalized epilepsy.

**Method:** Pediatric (<18 yr) and young adult (>18 yr) patients who underwent RNS implantation at Primary Children's Hospital in Salt Lake City, Utah were retrospectively identified and evaluated for operative complications, side effects, seizure burden, and quality of life (QOL) post-implantation.

**Results:** We identified 25 patients (20 pediatric and 5 young adult), ranging from 5-21 years of age at time of RNS implantation, with focal (11 [44%]), multifocal (11 [44%]) and generalized (3 [12%]) epilepsy. Operative complications (4 [16%]) and negative side effects (5 [20%]) were minor. Of the entire cohort, 14 (70%) pediatric and 4 (80%) young adult patients experienced improvement in seizure burden (1 [4%] seizure free, 4 [16%] ≥90% seizure reduction, 8 [32%] ≥50% reduction, 5 [20%] <50% reduction and 7 [28%] with no improvement). Of those with no improvement in seizure burden, RNS current not yet turned on in 4 (57%) patients due to recent implantation. Of the epilepsy types, 10 of 11 (91%) with focal epilepsy, 8 of 11 (73%) with multifocal epilepsy and 1 of 3 (33%) with generalized epilepsy experienced seizure reduction. Anti-seizure medication (ASM) reduced in 5 (20%) patients, rescue medication usage reduced in 8 (32%) patients and QOL improved in 13 (52%) of patients post-RNS implantation.

**Conclusion:** RNS implantation resulted in a reduction in seizure burden and improved QOL with minimal side effects in a majority of pediatric and young adult patients. Preliminary data from this small retrospective cohort suggests RNS may be an effective and safe treatment option for drug-resistant focal, multifocal, and generalized epilepsy in the pediatric population.

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**101 Lateralizing signs in patients with Hypothalamic Hamartoma**

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**Purpose:** Hypothalamic Hamartoma (HH) is a pharmacoresistant epileptogenic lesion. Stereotactic radiofrequency thermocoagulation (SRT) is a disconnecting intervention to treat HHs. MRI is the gold standard in unilateral HHs to determine the intervention side; no equivalent exists for bilateral HHs. We investigated defined parameters regarding their lateralization value to improve the presurgical evaluation of patients with bilateral HHs.

**Method:** We included 25 patients (2-55y) with uni- and bilateral HHs who underwent SRT and presurgical evaluation (2010-2020). We analyzed four parameters regarding their lateralization: ictal EEG, interictal epileptiform discharges during sleep and wakefulness (IEDs, IEDu) and semiology. The correlation between those and the HHs’ attachment side was calculated (Spearman’s \( \rho \)). Areas under the receiver operating characteristic (ROC) curves (AUC) and cut-offs were calculated for the left and right IEDs to define their prognostic lateralizing value. The difference \( \text{IED}_{\text{right}} - \text{IED}_{\text{left}} \) was plotted in an ROC curve, determining the required preponderance of unilateral IEDs to differentiate between left and right HH. Binomial logistic regression predicted the HHs’ attachment side.

**Results:** All parameters correlated strongly with the HHs’ attachment side (ictal EEG \( R=0.51, p=0.026; \) IEDs \( R=0.55, p=0.006; \) IEDu \( R=0.61, p=0.005; \) semiology \( R=-0.62, p=0.001 \)). The AUC was 0.76 for right IEDs (\( p=0.039 \)) and 0.85 for left IEDu (\( p=0.0074 \)). Cut-offs were 0.34 and 0.15. The AUC for \( \text{IED}_{\text{right}} - \text{IED}_{\text{left}} \) was 0.98 (\( p=0.0001 \)), the cut-off 0.16. In the regression model IEDs and semiology were significant coefficients and 88% of HHs were lateralized correctly.

**Conclusion:** IEDs can be useful biomarkers to lateralize the HH. If >50% of IEDs occur unilaterally, the HH is most likely attached ipsilaterally. Regarding predominantly bilateral IEDs, a slight preponderance of unilateral IEDs is sufficient to reflect the attachment side. Furthermore, the combined analysis of IEDu and semiology predicts the HH lateralization. The results require confirmation through a study focusing exclusively on bilateral HH.
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Seizure patterns from temporal lobe stereoEEG recordings are associated with postsurgical seizure outcome

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Temporal lobe epilepsy (TLE) is the commonest form of difficult-to-treat focal epilepsies. In 30-40% of cases with complex clinical manifestation or non-lesional MRI, the seizure onset zone can be defined best with invasive intracranial recordings. An inherent challenge of intracranial EEG recordings, however, is the spatial sampling bias, underscoring the need for reliable EEG biomarkers of the seizure-onset zone. Here, we aimed at identifying specific ictal patterns assessed by intracranial EEG electrodes which are linked to a favourable postsurgical seizure outcome in TLE.

In a retrospective study we re-evaluated stereoEEG recordings from 25 TLE patients, 20 of which were explored bi-temporally, and searched for stereoEEG biomarkers that correlated with post-surgical outcome. Thirteen patients displayed a good postsurgical seizure outcome (ILAE-Class 1-2; lesions: HS 6, other 4, non-lesional 3 ), and 12 patients an unfavorable outcome. A total of 152 seizures were analysed. All patients demonstrated a unilateral seizure onset. In 60%, seizures spread to the contralateral temporal lobe mesial structures. Seizures recorded in both temporal lobes showed a typical mesial temporal lobe ictal pattern. Clinically, most seizures presented with temporal semiology. In 11 patients focal to bilateral tonic-clonic motor seizures were observed. In all patients with good outcome, a particular pathological pattern (P-pattern, Gnatkovsky et al., 2019) was observed at seizure onset. This pattern was characterized by 10-40 s low voltage fast activity with a characteristic spectral fingerprint (chirps) and a short bursting phase at the end. In unfavorable post-surgical seizure outcome group, this specific P-pattern was absent, indicating rather an extratemporal seizure onset and more complex epileptogenic network. Intriguingly, patients in this group were mostly without apparent MRI lesion (HS 1, other lesions 2, non-lesional 9).

The results of study strengthen the potential role of specific seizure patterns to distinguish primary from secondary temporal lobe involvement in seizure generation.

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Strategies to optimize the surgical outcome of patients with drug resistant epilepsy and malformations of cortical development

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Purpose: There are limited studies that have evaluated the outcome of surgery for drug resistant epilepsy and malformations of cortical development.

Method: Between 2011 and 2021, 470 people with drug resistant epilepsy underwent surgery at NIMHANS, Bangalore, India. Malformations of cortical development (MCD) as underlying substrate have been identified among 147 people with epilepsy (PWE). Factors influencing the surgical outcome were studied.

Results: Cohort consists of 147 patients with Mean age at onset of epilepsy 3.38 ± 3.16 (SD) years (Median 4.29 (range; 2 days after birth to 40 years). Males constituted 66.7% of patients (n= 82). The duration of epilepsy before surgery had a range of 1- 32 years, with Mean of 9.47 ± 7.51 (SD) and Median of 11 years. Patients were operated at a Mean age of 16.85 ± 10.68 (SD) years with a Median of 14.33 years (range 2-58 years). Mean Seizure score of the cohort was at 8.40 (SD 1.38) with Range of 3-12 on a possible range of 0-12, i.e., 73.2% of patients had score of 3 to 5 which falls under 1-6 seizures/week to 4-10 seizures/day. 75 patients (60.5%) had FCD, 22 (17.86%) patients had DNET, and 10 patients (8.13%) had Ganglioglioma as cause of their DRE. At a follow up ranging from 1-107 Months with a Mean of 36.26 ± 24.48 (SD) Months i.e., a mean of 3.08 2.01 years (SD) with a range of 1-8.91 years, overall cohort (n=118, with 5 patients lost to follow-up) had an Engel outcome class Ia, I, II, III and IV of 71.11%, 80.50%, 9.32%, 5.93% and 4.23% respectively.

Conclusion: Three variables influence the outcome towards favorable arm of Engel class Ia. These factors are histopathology of FCD with balloon cells, Glioneuronal variant of MCD i.e., DNET/GG, and finally a younger age (less than eighteen years) of patients at surgery.
Efficacy of cardio-responsive vagal nerve stimulators in refractory epilepsy - a retrospective review

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Purpose: Vagal Nerve Stimulation (VNS) devices have been used for refractory epilepsy since 1997. There is a good body of evidence demonstrating their efficacy in this patient group. Since 2015, novel Cardio-Responsive devices were introduced to practice, promising additional benefit to the original VNS devices. There is limited literature reviewing their efficacy. This study aims to assess if patients with refractory epilepsy receive additional benefit from novel cardio-responsive VNS devices compared with traditional VNS devices.

Methods: Data was collected retrospectively from patients with epilepsy who had an existing VNS device, deemed to have been beneficial, which was then replaced with a new Cardio-responsive VNS. The two models being evaluated in this study are the SenTiva™ M1000 and AspireSR® 106. These battery changes occurred over a 4 year period from September 2016 to January 2021, carried out by a single surgeon. The seizure burden was compared between the periods before and after the battery change from traditional VNS to novel cardio-responsive VNS device.

Results: 65 patients were included in this review. There was a significant decrease in seizure burden from a median monthly seizure frequency of 16.3 (IQR 4.5-39.0) to 9.0 (IQR 3.0-30.3), p =0.01. When separated by seizure type, there was a non-significant decrease in median monthly tonic-clonic seizures from 1.0 (0.0-5.0) to 0.0 (0.0-4.3), p=0.06. Prior to battery change 42% had no tonic-clonic seizures, after battery change 54% had freedom from tonic-clonic seizures. 45% of the total cohort had ≥ 50% reduction in overall seizure frequency, contributing to a total of 57% showing a further reduction in seizure frequency following battery change (11% showed no change, 32% showed an increase in seizure frequency).

Conclusion: The results suggest that novel Cardio-responsive VNS devices further reduce seizure frequency for the majority of those already receiving successful treatment with traditional VNS devices.

How confident can we be when making personalised predictions of outcome after epilepsy surgery in children?

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Purpose: Neurosurgery is a safe and effective form of treatment for select children with drug-resistant epilepsy. There is, however, still potential to improve the selection of surgical patients, as post-operative seizure freedom rates range from as low as 14% to as high as 93% (West et al., 2019). To this end, we developed a predictive model of seizure outcome after epilepsy surgery in children, which can support surgery candidate selection and inform family counselling.

Method: We performed a retrospective cohort study of children referred for epilepsy surgery at a single, tertiary centre - Great Ormond Street Hospital - between 1 January 2000 and 31 December 2018. We collected demographic information, epilepsy characteristics, surgery details, neuroimaging findings, genetic results, histopathology diagnoses, 1-year post-operative seizure outcome and anti-seizure medication status. We used a multilayer perceptron classifier to predict seizure outcome. To accurately represent the clinical experience, only pre-surgical and surgical factors were included as features in the model.

Results: 873 children (461 males, 412 females) were identified as having undergone surgical resection or disconnection during the 19-year study period. Mean age at epilepsy onset was 2.8 years (SD=3.3 years) and mean age at surgery 8.9 years (SD=5.2 years). Excluding palliative procedures, 67% of patients were seizure-free (including no auras) and 15% of these were on no anti-seizure medication at 1-year follow-up. The classifier achieved an overall accuracy of 70%. Interestingly, the accuracy of the classifier varied by type of surgery performed, lobe operated on, and pre-operative neuroimaging findings. For example, the classifier had an accuracy of 86% for encephalitis, but only 33% for non low-grade tumours.

Conclusion: We present a model capable of delivering individualised predictions of post-operative seizure outcome, using only variables available at the time of pre-surgical evaluation. We will next investigate whether adding quantitative neuroimaging features improves model accuracy.
Academic attainment following epilepsy surgery in childhood: a systematic review

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Purpose: Frequent seizure activity can disrupt literacy and numeracy acquisition during important developmental windows. As a result, school-aged children with epilepsy are placed at significant risk of poor academic attainment. While the many cognitive changes that can occur following epilepsy surgery have been well-documented, the effect of surgical intervention on attainment is less understood. The aim of this systematic review is to identify the potential influence of epilepsy surgery on the core academic skills of reading, spelling and arithmetic.

Method: Four electronic databases were searched for studies investigating academic attainment after epilepsy surgery in childhood over the last three decades. 1987 articles were screened for relevance. Eleven studies met inclusion criteria.

Results: Results predominantly indicate that academic attainment scores are maintained at pre-operative levels approximately one year after epilepsy surgery. Though two cohorts did report significant declines in reading accuracy and/or arithmetic, these studies noted that attainment scores were maintained at pre-operative levels in the surgical group but continued to decline in the refractory, non-surgical group. Site and side of surgery did not influence findings in any of these studies. Cessation of anticonvulsant medication and older age at onset and at surgery correlated significantly with higher reading scores.

Conclusions: This review suggests that attainment scores are maintained at pre-operative levels following epilepsy surgery. As seizures often persist in the early stages of recovery and anti-convulsant medications are maintained, changes to learning ability would not be anticipated immediately after surgery. Still, this review indicates that children in their first year post-surgery do not generally show a decline in attainment skills previously acquired. Findings highlight the importance of timely access to surgery in order to relieve the burden of regular seizures and reduce anticonvulsant medications. Further research is necessary to fully understand the implications of epilepsy surgery timing on long-term academic attainment.

The proportion of seizure onset zone contacts resected is not associated with outcome following SEEG-guided resective epilepsy surgery in children

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Purpose: Children undergoing SEEG-guided epilepsy surgery represent a complex cohort. We aimed to determine whether the proportion of putative seizure onset zone (SOZ) contacts resected is associated with seizure outcome in this cohort.

Method: Patients who underwent SEEG-guided, resective epilepsy surgery over 6-years were included. The proportion of SOZ contacts resected was determined by co-registration of pre- and post-operative imaging. Seizure outcomes were classified as seizure-free (Engel class I) or not-seizure-free (Engel classes II-IV) at last follow-up. Patients without sufficient imaging (either pre- or post-operative) were excluded from primary analysis but were included in a sensitivity analysis to determine primary analysis' robustness.

Results: Twenty-two eligible patients were identified (median age at surgery of 10 years, range 5-18). Fifteen (68.2%) were seizure-free and 7 (31.8%) not (median follow-up of 19.5 months, range 3-46). On univariate analysis, histopathology, classified into focal cortical dysplasia (FCD), non-diagnostic status (NDS) and hippocampal sclerosis, was the only significant factor associated with seizure freedom (SF) (p=0.01). On post-hoc analysis, NDS significantly associated with non-SF (p=0.01), and FCD with SF (p=0.046). Factors including SOZ location, type of surgery, SEEG indication, epilepsy duration, follow-up duration, total number of SEEG contacts and non-SOZ SEEG contacts resected did not significantly associate with SF. The percentage of defined SOZ contacts resected ranged from 25-100% (median 78.3%) and was not associated with SF (p=0.89). In a binary logistic regression model, none of the included factors were independently associated with SF. On a sensitivity analysis of 29 patients, all univariate and binary logistic regression model findings from the primary analyses were confirmed.

Conclusion: Histopathology is a significant predictor of surgical outcomes in children undergoing SEEG-guided, resective epilepsy surgery. The percentage of SOZ contacts resected was not associated with SF. Other factors such as the neurophysiological definition of SOZ contacts may therefore play an important role.
Epileptogenic network definition through game theory and connectivity dynamics

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Purpose: Presurgical workups for treating drug-resistant epilepsy (DRE) patients do not ensure favorable outcomes. Stereo-EEG (SEEG) is a valuable resource for defining the epileptogenic network (EN). However, SEEG quantification is non-standardized, largely due to the lack of consensus regarding the EN concept. No strategy so far provided consistent results of surgical outcome prediction. We propose a generalizable model to detect ENs through changes in connectivity states. The underlying hypothesis is that the EN competes with non-epileptogenic networks to control brain dynamics through connectivity change between regions. The competition is constant, but the maximal change is measured around seizures, when the EN prevails.

Method: Connectivity measures were quantified at various intervals from interictal to ictal time. Connectivity change was quantified as classification performance of a machine learning algorithm applied to distinguish interval epochs. A game-theory rule, maximin, was used to identify the network with the greatest connectivity change. The overlap between the selected network and the resection was used to classify surgery outcomes. The framework was validated on a chronological cohort of 21 DRE patients, with the only inclusion criterion of a minimum 3-year follow-up.

Result: Surgical outcome prediction accuracy of 93% was achieved, which is the best to our knowledge. Several time intervals prior and during seizure were tested. The optimal time interval for EN definition was at the transition from pre-seizure to seizure. Interestingly, the worst time for EN definition was the seizure itself.

Conclusions: The present ictogenesis model for localizing ENs was validated by reliable surgery outcome classification. The transition to seizure may serve as a potential electrophysiological biomarker of the EN. This computational framework allows EN topological definition, which may aid surgical decision-making. This project was funded by the FLAG–ERA JTC 2017 Human Brain Project, CAUSALTOPIMICS.

Resection of MEG and intracranial EEG bandpower abnormalities explain surgical outcomes in focal epilepsy

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Bandpower abnormalities relative to normative recordings in a cohort of epilepsy patients have been shown to relate to surgical outcome using intracranial EEG (iEEG) data (Taylor et al. Brain 2021 in press). However, it is unknown if cortical abnormalities derived from MEG also explain outcome. Using resting-state MEG recordings, we compute neocortical bandpower spatial maps for a cohort of normative individuals and patients living with epilepsy. We assess how well MEG predicts surgical outcome (ILAE1 vs ILAE2+) in isolation, and compare its predictive power to iEEG. Resting-state MEG and iEEG recordings for 29 epilepsy patients (temporal=13, extratemporal=16) were compared with normative relative bandpower maps (MEG=88, iEEG=234) to assess cortical bandpower abnormalities across five commonly used frequency bands. Patient and region-specific abnormalities were estimated as the maximum absolute z-score across all five frequency bands. Using post-operative MRI we identified resected and spared regions. We hypothesized resection of abnormalities in seizure-free patients.

For MEG, resected regions in seizure free patients were more abnormal than those spared. Distinguishability measures discriminated surgical outcome groups reasonably well across the whole cohort (AUC=0.667, p=0.082), and particularly well in extratemporal patients (AUC=0.782, p=0.045). In extratemporal patients MEG abnormalities outperformed iEEG abnormalities at discriminating outcome groups (AUC=0.700 p=0.117).

Our results demonstrate that resting-state MEG and iEEG bandpower abnormalities may predict surgical outcome groups well, with each modality providing potentially complementary information. This suggests that the harmonisation of MEG and iEEG data could be useful for localising epileptogenic tissue in patients who are candidates for surgical resection.
201 Long-term outcome following selective amygdalo-hippocampectomy in temporal lobe epilepsy: piriform cortex resection reveals superior seizure control rates

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Purpose: Transsyllavian selective amygdalo-hippocampectomy (tsSAHE) is a valid surgical treatment option for drug-resistant mesial temporal lobe epilepsy (mTLE). In a recently published study, we showed that resection of at least 27% of piriform cortex strongly correlated with seizure freedom one year following tsSAHE. However, the impact of piriform cortex resection on long-term seizure outcome is currently unknown. The aim of this study was to evaluate the impact of piriform cortex resection on long-term seizure outcome after tsSAHE.

Methods: Long-term follow-up (FU) was defined as at least two years postoperatively. Between 2012 and 2017, 64 patients with mTLE who had undergone tsSAHE at our center with a completed dataset for long-term FU were included in the analysis. Seizure outcome at the last available follow-up was assessed according to the International League against Epilepsy (ILAE). Patients were stratified according to favorable (ILAE class 1) and unfavorable (ILAE class 2-6) seizure outcome and resected proportions of hippocampus, amygdala and piriform cortex were volumetrically assessed.

Results: In the whole cohort, the mean FU duration was 3.75 years (yrs) (standard deviation ± 1.61 yrs). Patients with favorable long-term seizure outcome revealed a significantly larger proportion of resected piriform cortex compared to patients with unfavorable seizure outcome (median resected proportion was 46% (IQR 31-57) versus (vs.) 16% (IQR 6-38), p=0.001). Among those patients with at least 27% resected proportion of piriform cortex, there were significantly more patients with seizure freedom at the last FU compared to the patients with less than 27% resected proportion of piriform cortex (83% vs. 39%, p=0.0007).

Conclusions: Our results show a strong impact of the extent of piriform cortex resection on long-term seizure outcome following tsSAHE in mTLE. The authors suggest the piriform cortex to constitute a key target volume in tsSAHE to achieve seizure freedom in the long-term.

204 Epileptogenic tubers are associated with more homogeneous calcium content: a combined quantitative susceptibility mapping (QSM) and stereoelectroencephalography (SEEG) pilot study

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Purpose: Prior studies have found an association between calcification and epileptogenicity of tubers in tuberous sclerosis complex (TSC). Quantitative susceptibility mapping (QSM) is a novel tool which can quantify the magnetic susceptibility of tissue. In this explorative pilot study, we assess the utility of QSM in identifying putative epileptogenic tubers in TSC using stereoelectroencephalography (SEEG) data as ground truth.

Methods: We studied TSC patients undergoing SEEG who had multi-echo gradient-echo sequences available. QSM and R2* values were extracted for all tubers, based on manually drawn 3D regions of interest using 3D T1 and T2-FLAIR sequences. Characteristics of the distribution of QSM and R2* values from implanted tubers were compared using binary logistic generalised estimating equation (GEE) models designed to identify ictal (involved in seizure onset) and interictal (persistent interictal epileptiform activity) tubers. These models were then applied to the unimplanted tubers to identify potential ictal and interictal tubers that were not sampled by SEEG.

Results: A total of 146 tubers were identified in 10 patients, 76 of which were sampled using SEEG. The GEE models identified that higher kurtosis of the QSM values within each tuber was associated with epileptogenicity (p=0.04 for the ictal model and p=0.005 for the interictal model). Both models had poor sensitivity (35.0% and 44.1% respectively) but high specificity (94.6% and 78.6% respectively). When the models were applied to the unimplanted tubers, there was a linear association between the number of unresected ictal tubers and post-operative Engel outcome, although this was not statistically significant (p=0.16).

Conclusion: There was increased kurtosis of QSM values in epileptogenic tubers, indicating increased homogeneity of calcium content. This study provides an important proof of principle that quantification and assessment of tuber calcium content through QSM may be a useful biomarker in the identification of putative epileptogenic tubers in TSC.
The MAST Trial: prospective evaluation of a machine learning algorithm for the planning of SEEG trajectories

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Purpose: Despite a plethora of machine learning algorithms that have been developed in the field of epilepsy, few have undergone prospective clinical evaluation with a view to being integrated into routine clinical practice. Here, we report results of a prospective evaluation a lesion detection algorithm designed to detect focal cortical dysplasia (FCD) in children undergoing stereoencephalography (SEEG) at a single centre.

Methods: This prospective single arm interventional (IDEAL phase 1/2a) study of 20 patients. Children undergoing SEEG at a single centre were enrolled in the study. Following routine SEEG planning, clinical MRI scans were run through the MELD lesion detection algorithm to identify putative lesion clusters, which were merged with the planned electrode trajectories. If the top 3 MELD-identified lesion clusters were not already sampled, up to 3 additional SEEG electrodes were added. The primary outcome measure was the proportion of patients that had additional electrode contacts in the SEEG-defined seizure onset zone. Secondary outcomes included safety and efficacy end points.

Results: To date, 15 patients (median age 12.6, 7 females) have been recruited to the study, in whom a SOZ has been identified in 8 (53%). A total of 51 lesion clusters have been identified (range 0-11), of which 17 have fulfilled criteria for implantation. A total of 12 additional electrodes have been implanted in 7 patients. One (7%) has fulfilled the primary outcome measure whilst one other patient has had the SOZ identified within a cluster that was already implanted as part of the routine SEEG plan. There have been no safety issues.

Conclusion: We demonstrate early-stage prospective clinical validation of a machine learning lesion detection algorithm in aiding the identification of the seizure onset zone in children undergoing SEEG. Further multi-centre validation will build the rationale for incorporating such technology into routine clinical use.

Stereo-electroencephalography-guided radiofrequency thermocoagulation in patients with MRI-negative focal epilepsy

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Purpose: Coupled to stereo-electroencephalography, radiofrequency thermocoagulation (SEEG-RFTC) represents a therapeutic alternative for patients with refractory focal epilepsy, with highly variable outcome results across studies. Nonlesional MRI has been described as a predictor of unfavorable response. This work aims to describe the outcomes of SEEG-RFTC, focusing on patients with MRI-negative epilepsy.

Method: We conducted a retrospective observational study including 31 patients who were affected with MRI-negative focal epilepsy and submitted to SEEG-RFTC. Primary outcome was freedom from disabling seizures at last follow-up. Reduction in seizure frequency (a reduction of more than 50% was classified as RFTC-response) and neuropsychological outcomes were also evaluated. Potential factors influencing post-RFTC outcome were considered comparing different variables between responders and non-responders.

Results: The mean follow-up period was 27.2 months (range 6-69) and twenty-three patients (74.2%) completed a minimum follow-up period of one year. Fourteen patients (45.2%) were responders, showing eight of them seizure-freedom (25.8% of the whole cohort). All seizure-free patients at 6-month visit maintained their status during the long-term follow-up. One case had a permanent complication not directly related to thermolections. Most patients showed no significant change in cognitive profile. Electrically elicited seizures (EES) were observed in all seizure-free patients and were more frequent in responders (p=0.038).

Conclusion: SEEG-RFTC may lead to a good response also in patients with MRI-negative focal epilepsies; in our cohort, a quarter of the patients were seizure-free and almost one-half were responders at last follow-up. Although these results are still far from those achieved through conventional resective surgery, a non-negligible proportion of patients may benefit from this one-stage and much less invasive approach. Although factors associated with seizure outcome remain still to be elucidated, in our study EES were significantly more frequent among responders, and achieving a 6-month period of seizure freedom seems to predict a long-term good response.
Normative brain mapping of interictal intracranial EEG to localise epileptogenic tissue

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The identification of abnormal electrographic activity is important in a wide range of neurological disorders, including epilepsy for localising epileptogenic tissue. However, this identification may be challenging during non-seizure (interictal) periods, especially if abnormalities are subtle compared to the repertoire of possible healthy brain dynamics. Here, we investigate if such interictal abnormalities become more salient by quantitatively accounting for the range of healthy brain dynamics in a location-specific manner. To this end, we constructed a normative map of brain dynamics, in terms of relative band power, from interictal intracranial recordings from 234 subjects (21,598 electrode contacts). We then compared interictal recordings from 62 patients with epilepsy to the normative map to identify abnormal regions. We hypothesised that if the most abnormal regions were spared by surgery, then patients would be more likely to experience continued seizures post-operatively. We first confirmed that the spatial variations of band power in the normative map across brain regions were consistent with healthy variations reported in the literature. Second, when accounting for the normative variations, regions which were spared by surgery were more abnormal than those resected only in patients with persistent post-operative seizures (t=-3.6, p=0.0003), confirming our hypothesis. Third, we found that this effect discriminated patient outcomes (AUC=0.75 p=0.0003). Normative mapping is a well-established practice in neuroscientific research. Our study suggests that this approach is feasible to detect interictal abnormalities in intracranial EEG, and of potential clinical value to identify pathological tissue in epilepsy. Finally, we make our normative intracranial map publicly available to facilitate future investigations in epilepsy and beyond.

A retrospective review of the pathology of epilepsy surgeries at a tertiary referral centre in Ireland

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Purpose: About 33% of epilepsy patients have seizures that cannot be controlled with medication. For selected patients, resection of epileptogenic brain has a better chance of controlling drug-resistant seizures than further medication trials. As part of patient care, an electronic patient record (EPR) is maintained on all patients treated at Beaumont Hospital (Ireland) with epilepsy. It was noted that the pathology of epilepsy surgeries was often not readily available on the EPR.

Methods: We conducted a retrospective review in our epilepsy clinic using the EPR to determine the frequency with which the pathology of epilepsy surgeries were documented, with the aim of ultimately improving documentation. In cases where pathology was not documented, patient charts and pathology lab reports were analysed. Cases of focal cortical dysplasia (FCD), in particular, were phenotyped to determine which cases were still refractory post-surgery (with a particular focus on Type II for consideration for treatment with everolimus).

Results: 280 cases have been analysed to date. 107/280 (38.2%) had the pathology of epilepsy surgery documented, while 173/280 (61.8%) were not. There were 75 (27%) cases of tumour-related pathology, 12 (4%) vascular malformations, 26 (9%) hippocampal sclerosis, 70 (25%) gliosis, 64 (23%) normal or inconclusive pathology, while there were 32 (11%) cases of malformations of cortical development (MCD). This includes 23 (8%) cases of FCD (Types I, II, III), 15 (5%) of which were Type II. 7/15 were patients with ongoing, refractory epilepsy.

Conclusion: The pathology of epilepsy surgery is an important factor in the success of surgery. However, documentation levels in this review were below 50% (less than half). The FCD cohort thus far represents 8.2% of the pathology identified. This is comparable to the reported 9% in the literature. Further research on the use of everolimus as an adjunctive therapy in these patients is ongoing.
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SEEG-guided radiofrequency thermocoagulation in refractory focal epilepsy

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Purpose: RFTC is a minimally invasive ablative option for refractory focal epilepsy. Our aim was assess effectiveness and safety of SEEG-guided radiofrequency thermocoagulation in refractory focal epilepsy.

Methods: A retrospective chart review was conducted of all patients who underwent stereo EEG- guided RF-TC at our center. Total number of patients with follow-up more than 6 months were 49.

Results: The mean age of onset was 24,2 years and the mean age at SEEG was 35,2 years. MRI lesions were not identified in 65 % of the series. 56.5% of the patients were seizure free at 1 month. The mean duration of improvement was 4.8 months. 4 patients were seizure free for >12. 4 patients had functional deficits post-procedures, transient in 3 patients and prolonged in one of whom. 3/4 were anticipated following the results of cortical stimulation. Multivariate analysis found 2 independent criteria linked to RFTC efficiency one month after RFTC: frequency of the seizures before RFTC and number of contacts used.

Conclusion: RFTC is a safe method providing important predictive information for surgical resection. An improvement in seizure frequency, often transient, is seen in 2/3 of our patients. RFTC could be useful as a palliative technique for patients with an epileptogenic zone overlapping with eloquent areas, with minimal risk of complications.

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Lesion-focused stereotactic radiofrequency thermocoagulation for bottom of sulcus focal cortical dysplasia: Case series and call for prospective registry study

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Purpose: Minimally invasive surgical treatment options are increasingly used in epilepsy surgery. We describe our experience with lesion-focused stereotactic radiofrequency thermocoagulation (L-RFTC) for bottom of sulcus focal cortical dysplasia (BOS-FCD) since 2012, and propose a multicenter prospective registry study to compare this method to open resections.

Method: Retrospective case series of 13 patients (6 women, median age 32 years) treated with L-RFTC from 2012 to 2019. Patients were offered both L-RFTC and open resection of small BOS-FCD after comprehensive noninvasive and intracranial (n=7) presurgical epilepsy evaluation suggested that the BOS-FCD was the epileptogenic zone. Planning of the L-RFTC was done based on 3D-FLAIR-MRI in order to achieve complete destruction of the BOS-FCD through a series of coagulations using up to 7 trajectories.

Results: Locations of BOS-FCD were superior frontal in 4, central in 3, insular in 2, parietal in 2, and orbitofrontal and tempororooccipital in one patient each. In 10 cases, the BOS-FCD was located in or adjacent to eloquent cortex. One patient underwent further open resection for unchanged seizure frequency six months after L-RFTC. Seizure outcome at 12 months was Engel I in 11 and Engel II in 2; at 24 months Engel I in 8, Engel II in 2, and not available in 3. Last observed outcome after 34 months (mean) / 26 months (median) was Engel I in 7, Engel Ib in 3, Engel 2 in 2, and Engel 3 in 1. There was one postprocedural ischemia adjacent to the coagulation cavity, resulting in permanent left hand sensory impairment and subtle gait ataxia.

Conclusion: L-RFTC is a minimally invasive treatment option that can be an alternative to an open resection in selected patients with small BOS-FCD. We propose a multicenter prospective registry study to investigate whether this method can be applied in a broader setting.
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Use of laser interstitial thermal therapy for pediatric TSC-associated epilepsy with multiple tubers

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Purpose: Tuberous sclerosis (TSC) causes seizures in ~85% of patients. Drug resistance, multiple seizure types, discordant findings in video-EEG studies, and multiple tubers are common occurrences in these patients, which have limited the use of resective epilepsy surgery due to its invasiveness. We therefore investigated the value of MR-guided LITT following stereotactic intracranial EEG (sEEG) in this patient population.

Methods: We started an algorithm of sEEG followed by LITT using the Medtronic Visualase system in January 2021 and recorded patient and procedural data in a prospectively kept database. SEEG-electrodes and laser fibers were implanted in a surgical suite equipped with intraoperative MRI using a frameless stereotactic approach with and without robotic guidance.

Results: In the first year after implementing this algorithm, we treated 7 pediatric patients with 8 LITT procedures. All patients had multiple tubers (range 9 to >30) and no single dominant tuber could be defined using prolonged video scalp-EEG. For sEEG we implanted a median of 10 electrodes (range 8-14) per patient. All patients showed interictal epileptiform activity on multiple electrodes, but ictal activity was more confined in most cases. Six procedures used two laser fibers and two procedures only one. A mean energy of 4610.6 joule (SD±1836.7 joule) per fiber was used to create a mean ablation volume of 12.1 cm³(SD±6.9 cm³) per patient. One patient showed transient increase of a preexisting hemiparesis, which resolved under corticosteroid treatment; otherwise, there were no complications. LITT led to a decrease of seizure frequency in all patients and the patients’ caregivers noted developmental improvements.

Conclusion: LITT following sEEG is a valuable tool for TSC-associated epilepsy, especially in patients not considered good candidates for a resective surgery. Even though long-term outcome data is still missing, the success seen so far warrants continuation and further investigation of this treatment algorithm.

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Start of laser ablation (LiTT) in Spain: initial report of two reference centers

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Purpose: The laser ablation technique (LiTT) offers new opportunities in epilepsy surgery. Performing MRI-controlled destruction of tissue with control of temperature and limits is not offered by other techniques such as RF-CT. We report the preliminary experience with LiTT in adult patients of two national and European reference centers (EPICare) in Spain.

Method: 18 procedures have been performed in 16 adult patients: 4 hypothalamic hamartomas (HH), 4 hippocampal sclerosis (HS), 1 complex periventricular heterotopia (PVH), 3 incomplete resection remnants, 1 posterior quadrant cystic lesion in neurofibromatosis type 1 (NF1), 1 low-grade neuroglial tumor, 1 tuberous sclerosis complex (TSC) and 1 sulcus bottom dysplasia (FCD). Specific protocols were developed for each pathology. The implantations were performed using a robot and the ablations were performed in the Neuroradiology Department. The indication was made in a multidisciplinary meeting.

Results: In all 18 ablations there was 1 complication (hemianopia) and all patients were discharged 48-72 hours after the procedure. A suboptimal catheter trajectory was detected in 4 out of 15 ablations. Analyzed by pathology, the patient with low-grade neuroglial tumor, 3 out of 4 patients with HS and 1 patient with FCD are seizure free (Engel I). 2 patients with HH have presented a seizure reduction of 80% (Engel II). The patient with HPV presented an initial seizure reduction of 80% but relapsed posteriorly (Engel III). Only 1 out of 3 patients with surgical remnants was seizure-free (Engel I). Out of 10 cognitive evaluations, 3 improved, 5 were unchanged and 2 worsening were detected.

Conclusion: LiTT is a safe procedure with good tolerability and suitable for use in complex cases, but also in TLE when the cognitive outcome is a concern. LiTT requires high hospital resources. Results are excellent in some indications but poor in others. The main complications arise from suboptimal catheter trajectories.
Be Aware: the safety of temporarily pausing propofol to enable intraoperative electrocorticography during epilepsy surgery under general anesthesia

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Purpose: The administration of propofol could be paused during epilepsy surgery under general anesthesia to improve intraoperative electrocorticography signals. We evaluated the safety of this procedure regarding the depth of sedation and the risks of awareness.

Method: We retrospectively included surgeries in which the propofol administration was paused to record electrocorticography. Clinical reports were screened for signs of awareness. We used intraoperative motor movements and the change of vital signs during surgery as indicators of the depth of sedation. We calculated the change of mean arterial blood pressure (MAP) and heart rate (HR) during the propofol pause compared to the baseline. The baseline was defined as the mean MAP or HR ten minutes before the propofol pause. MAP and HR increase of more than 15% were considered clinically relevant. We investigated whether clinical factors such as the ASA physical status classification (ASA class) predicted clinically relevant MAP and HR increase using the logistic regression model and expressed the predictive value in odds ratio with 95% confidence interval (OR, 95% CI).

Results: We included 352 surgeries in which propofol was paused 742 times. The average duration of the pauses was 9 ± 5 minutes. Five patients moved during the pause. One of them had relevant MAP and HR increase. Four patients had relevant MAP and HR increase without motor movements. No patients reported awareness. Increased duration of the propofol pause and ASA class III predicted clinically relevant MAP and HR increase (respectively: OR=1.12, 95%CI[1.05 – 1.19], OR=3.85, 95%CI[1.05 – 14.17]).

Conclusion: Adequate depth of general anesthesia could be maintained when the administration of propofol was paused during epilepsy surgery. The benefits of optimal epilepsy surgery outweighed the limited potential risks of this approach. Temporarily pausing the administration of propofol could be considered safe when using MAP and HR as proxies for potential arousals.

Preoperative anxiety predicts postoperative satisfaction in epilepsy surgery

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Purpose: Patient reported outcome measures (PROMS’s) are an important metric in the assessment of outcomes following any elective treatment. The Epilepsy Surgery Satisfaction Questionnaire (ESSQ-19) is a validated measure of patient satisfaction that yields a global satisfaction score and scores in four further sub domains; seizure control, psychosocial function, surgical complications and recovery from surgery. Post operative factors such as seizure freedom and reductions in anti-seizure medications have been associated with increased satisfaction ratings on these indices following surgery, however, the influence of preoperative factors has not yet been explored. This study examined preoperative psychiatric predictors of ESSQ-19 scores.

Methods: All patients who underwent epilepsy surgery at our center in the decade between January 2010 and 2020 and who were at least one year out from surgery were invited to complete the ESSQ-19 (n=284).

Results: Responses were received from 29% of the sample. Non responders did not differ from responders in age, type of surgery, sex or seizure outcome, but had a lower verbal intellectual function. Reported satisfaction rates were high in each ESSQ-19 domain (Seizure control, mean = 83.9; Psychosocial function, mean = 72.4; Surgical Complications, mean = 86.4; Recovery from surgery, mean = 77.4; Overall satisfaction, mean =80.8) and broadly comparable to those reported in the original validation sample. Preoperative levels of anxiety predicted postoperative satisfaction with recovery from surgery and psychosocial outcomes, with higher levels of anxiety associated with higher levels of dissatisfaction in both sub domains.

Conclusions: Satisfaction with some aspects of postoperative outcome is not just dependent upon postoperative factors but can be predicted from preoperative levels of anxiety. Clinicians offering preoperative counselling and preparation with respect to patients’ expectations of surgical outcome should be cognizant of the possible impact of anxiety on postoperative satisfaction, particularly with respect to psychosocial function.
Clinical utility of semi-automatic electric source imaging of interictal discharges powered by Epilog in presurgical evaluation and surgical treatment decision making

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Purpose: EEG source imaging (ESI) has an additive value in about one-third of the patients with drug resistant focal epilepsy (Foged M et al. Clin Neurophysiol 2020;131:324-329). We aimed to evaluate clinical utility of the automated ESI analyses results during presurgical work-up.

Methods: Thirty consecutive presurgical patients (mean age of 33.8 years (range 3.8-56.6)) with focal onset epilepsy during 2021 were included. The video-EEG recorded at the Kuopio University Hospital was analyzed using Epilog NV services (Gent, Belgium). Automatically detected spike clusters were evaluated and the source localization at the half-rising phase of the peak of the averaged spikes was used for the ESI localization on the lobar level. The reports of the epilepsy surgery team meetings, which included summary of the clinical, antiseizure medication, genetic, MRI, MEG and FDG-PET data, were used for the assessment of the clinical utility of the ESI results in the decision making process during presurgical evaluation. We present the preliminary results.

Results: Epilepsy duration was 17.8 ±12.7 years. MRI abnormalities were detected in 22/30 patients and FDG-PET hypometabolism – in 19/27 patients. In the automated ESI analyses no spikes or no true epileptic spikes were detected in four patients (13%). The largest spike clusters (average 1998 spikes/cluster) were localized to temporal (16), frontal (7) lobes or insula (3). Overall, two patients refused to continue with presurgical evaluation. Preliminary decision of the multidisciplinary team: seven surgical resections, three vagal/DBS stimulator implantations, for eight no surgical treatment, for ten the clinical decision is still pending.

Conclusions: Automated spike detection analyses and source localization performed using commercial Epilog platform identified true epileptic spikes in 26/30 consecutive presurgical patients thus leaning the process of interictal analyses of the video-EEG monitoring. The detailed evaluation of the clinical utility of the identified ESIs for presurgical evaluation and decision-making will be presented.

The spatial relationship between the MRI lesion and intraoperative electrocorticography in focal epilepsy surgery

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Purpose: MRI and intraoperative electrocorticography are often used in tandem to delineate epileptogenic tissue in focal epilepsy surgery. The aim of this study was to find the spatial relationship between MRI lesions and electrophysiological discharges on electrocorticography, e.g., spikes (<80Hz) and ripples (80-250Hz).

Method: We retrospectively included 33 pediatric and adult patients with lesional neocortical epilepsy who underwent electrocorticography-tailored surgery (14 female, median age=13.4 years, range=0.6-47.0 years). Mesiotemporal lesions were excluded. We used univariate linear regression to find correlations between spike/ripple rates on an electrode and its distance from the MRI lesion. We tested distances to three different points of the lesion. A simple slopes moderator analysis was used to investigate whether and how the underlying pathology type and lesion volume influenced any existing correlations.

Results: We found spike and ripple rates to be spatially most strongly linked to the edge of the MRI lesion. The underlying pathology type markedly influenced the spatial relationship between event rates and the MRI lesion (pspikes<0.0001, pripples<0.0001), while lesion volume did not (pspikes=0.64, pripples=0.89). A higher spike rate was associated with a shorter distance to the lesion for cavernomas (B=-1.37, p<0.0001, η²=0.22), focal cortical dysplasias (B=-0.25, p<0.0001, η²=0.05), and pleomorphic xanthoastrocytomas (B=-0.18, p<0.01, η²=0.09). For focal cortical dysplasias, a higher ripple rate was also associated with a shorter distance (B=-0.35, p<0.001, η²=0.05). Conversely, low-grade gliomas showed a positive correlation; the further an electrode was away from the lesion, the higher the rate of spikes (B=0.65, p<0.0001, η²=0.37) and ripples (B=2.67, p<0.0001, η²=0.22) recorded on it.

Conclusion: Pathophysiological processes specific to certain pathology types seem to determine the spatial link between the MRI lesion and event rates in electrocorticography. This should be considered when interpreting electrocorticography results intraoperatively. This study also supports previous findings that non-tumorous lesions intrinsically generate spikes and ripples, while low-grade tumours preferentially cause epileptogenicity in the peritumoral tissue.
Retrospective study of single pulse electrical stimulation (SPES) as a clinical tool during intracranial presurgical evaluation for drug resistant epilepsy

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Introduction: Cortical responses to single pulse electrical stimulation (SPES) have been used as part of the pre-surgical assessment workup during intracranial telemetry, to assess cortical hyperexcitability and connectivity between different brain areas.

Methods: We retrospectively studied 358 patients from 1999-2019 who had undergone SPES during presurgical intracranial telemetry at King’s College Hospital. To evaluate the clinical value of SPES, we studied surgical outcomes of 107 patients who underwent resective surgery with a follow-up of >12 months. We classified outcome into patients with temporal and extratemporal resections. Patients with previous cortical resection were excluded from this analysis. Engel I-II was considered as favourable surgical outcome.

Results: Seventy-seven patients had temporal resection. Among the 55 with favourable outcome (71% out of the total with temporal resections), 36 (65%) had a complete resection and 10 (18%) had partial resection of the areas of SPES abnormalities. Nine (16%) did not show abnormal responses to SPES. Among the 22 patients with unfavourable outcome, seven (32%) had complete resection of the areas of SPES abnormalities, 10 (45%) had partial resection, and five (23%) did not show SPES abnormal responses.

Thirty patients were operated over extratemporal regions. Among the 13 patients with favourable outcome (43% of the total with extratemporal resections), five (38%) had a complete resection and three (23%) had a partial resection of the SPES abnormal areas. Five (38%) did not show abnormal responses to SPES. Among the 17 patients with unfavourable outcome, one (6%) had a complete resection of the SPES abnormalities and 11 (65%) had not resected SPES abnormalities. Five (29%) did not show SPES abnormal responses.

Conclusion: Complete resection of areas with SPES responses showed a correlation with favourable surgical outcome. SPES could be considered as an additional useful investigation during the presurgical assessment workup in patients undergoing intracranial recordings.

Epilepsy surgery in Latvia: results of the first 5 years of prospective database

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Purpose: Epilepsy surgery can be extremely effective treatment in selected refractory epilepsy patient group. Studies have shown wide range (14-91%) of seizure freedom at different centers after resective procedures. Seizure freedom rates depend on several factors including experience and skills of the team. It is very important to follow results at local level to compare them with international data.

Method: Epilepsy surgery was introduced in Children’s Clinical University Hospital at Jan 2017. Prospective database (REDCap) of presurgical investigation, surgery and follow up program was made. Statistics: RStudio 1.3.1093.

Results: Epilepsy surgery was performed in 28 patients (age 0.4-34.0, mean 11.6 y, 24 children, 4 adults), 13 (46%) were temporal, 9 (32%) frontal, 3 (11%) temporo-occipital, 1 (3.6%) temporo-parietal, 1 (3.6%) parieto-occipital, 1 (3.6%) hemispherotomy; 13 (46%) were lesionectomies, 9 (32%) anterior temporal lobectomies, 2 (7.1%) lesionectomies plus cortectomies, 2 (7.1%) extended temporal lobectomies, 1 (3.6%) Delalande hemispherotomy, 1 (3.6%) lobectomy. By radiological etiology 18 (64.3 %) were MCDs (9 FCDs, 5 TSC), 5 (17.9%) gliosis/scarring, 4 (14.3%) low grade tumors, 2 (7.1%) had hippocampal sclerosis. Epileptic encephalopathies were diagnosed in 4 (14.3%) children.

Follow up time was 0.25-5 years (mean 1.5), 17 (61%) were seizure free (ILAE class 1 and 2) with 59% (95% CI: 43-81%) survival probability after 5 years. Repeated surgery was required for 5 (17.8%) patients.

Adverse events were recorded in 6 (21.4%) patients (isolated or in combination: 2 brain edema, 3 cerebral infarction, 2 hemi/monoparesis, 1 diplopia, 1 dysphagia). Permanent unexpected neurological deficit experienced 1 (3.6%) patient.

No statistically significant predictors of favorable outcome can be found at this point.

Conclusion: Larger patient group and longer follow up period is required to compare data with international datasets. Selected cases show that it is extremely important to have fast access to epilepsy surgery in every country.
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The hybrid 18F-FDG PET/MRI in pre-surgical evaluation of focal pediatric epilepsy: a multicentric study

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Purpose: To evaluate the role of hybrid 18F-FDG PET/MRI in the study of pediatric patients potentially candidate to epilepsy surgery.

Method: Multicentric retrospective study on pediatric patients with focal epilepsy, evaluated for epilepsy surgery from January 2017 to October 2021 (OPBG, Rome - Hospital of Padua). All patients underwent 18F-FDG PET/MRI. EEG was performed during radiotracer injection. Neuroradiological data were analysed based on the hypothesized epileptogenic zone (EZ). Phase1: blinded evaluation of 3T MRI data. Phase2: analysis of PET/MRI data. Phase3: agreement between neuroimaging results and hypothesized EZ was verified. EEG and metabolic changes were visually scored.

Results: 80 patients, mean age 9.5 years (0.7-18.4), disease duration 4.33 years (0.1-18.3). Hypothesized EZ: frontal (35%), temporal (27%), fronto-temporal (14%), other (24%). 21% of periprocedural EEG showed frequent abnormalities. Phase1: 36/80 MRI positive. Phase2: PET/MRI +/+ (47/80), PET/MRI +/- (22/80), PET/MRI -/+ (1/80), PET/MRI -/- (10/80). Phase3: agreement with the electroclinical hypothesis in 92% of positive cases from Phase1 (33/36), in 94% from Phase2 (65/69). Metabolic changes: 40% larger than lesion, 16% multilobar, 11% involving subcortical structures; 6% hypermetabolism. PET/MRI identified EZ in 86% of cases, 12 more lesions if compared with Phase1 (59% vs 45%). 26 patients underwent surgical resection, 4 thermocoagulation (70% Engel IA, mean FU 1.46 years); the others are not eligible or waiting for surgery.

Conclusion: The 18 F-FDG PET/MRI analysis of data revealed an improved diagnostic capability in identifying EZ concordant with the electro-clinical hypothesis, if compared with the blinded 3T MRI, and with the 3T MRI co-evaluated with PET. Few similar studies have been reported in pediatric cohorts (Oldan JD et al. Seizure 2018;61:128-134; Paldino et al. Pediatr Radiol 2017;47(11):1500-1507; Guo K et al., Eur Radiol 2021;31(9):6974-6982). Our study supports the role of hybrid 18 F-FDG PET/MRI in pre-surgical evaluation of pediatric patients with focal epilepsy.

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Implantation and reimplantation of intracranial EEG electrodes in patients considering epilepsy surgery

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In patients with drug-resistant epilepsy who are considering surgical therapy, intracranial EEG (iEEG) helps delineate the putative epileptogenic zone. In a minority of patients, however, iEEG fails to identify seizure onsets. In such cases, it might be worthwhile to reconsider the original hypotheses regarding the location of the seizure onset zone and to reimplant more iEEG electrodes to sample additional cerebral regions. The consequences of such a strategy for the patient are unknown.

In this retrospective, single-center case-control study, we identified ten patients in whom the initial set of implanted iEEG electrodes did not allow delineating the seizure onset zone precisely enough to offer resective surgery, and in whom additional iEEG electrodes were implanted in a second operation within the same hospital stay (leaving in place most or all of the initially implanted electrodes). These cases were matched to controls who did not undergo reimplantation with respect to duration of epilepsy, temporal vs. extra-temporal lobe epilepsy, and presence or absence of a putative epileptogenic lesion on the MRI. Seven cases and eight controls went on to resective surgery. No intracranial infection occurred in either cases or controls. One control suffered an intracranial hemorrhage. 3 cases and 2 controls suffered from a post-operative neurological or neuropsychological deficit (difference not statistically significant). Most importantly, we found no difference in post-operative seizure control between cases and controls (mean ILAE score difference 0.2, p=0.75). Compared to an ILAE score of 5 (i.e. stable seizure frequency in the absence of resective surgery), our cases showed significant improvement (mean ILAE score difference -1.3, p=0.013). Despite our small sample size, our study suggests that reimplantation of iEEG electrodes can offer the possibility of epilepsy surgery to patients in whom the initial iEEG investigation was inconclusive, without compromising on the risk of complications or on seizure control.
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Twenty-five years of epilepsy surgery at a Central European Center – trends in intervention delay and outcomes

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Purpose: This study aimed to analyze changes in the outcomes, intervention delay, and disease characteristics in patients referred to Brno Epilepsy Center for epilepsy surgery over the last twenty-five years.

Method: A total of 605 patients with pharmacoresistant epilepsy who underwent intracranial epilepsy surgery or VNS implantation were enrolled in the study. Three periods were compared statistically (1995-2000, 2001-2010, and 2011-2020). Engel class I was considered a successful outcome for intracranial surgery, McHugh class I or II for VNS implantation.

Results: In total, 384 patients underwent intracranial surgery and 221 patients a VNS implantation. In the three analyzed time periods, the duration of epilepsy before referral to the center has not decreased (17, 18.2, and 18.1 years for 1995-2000, 2001-2010, and 2011-2020 respectively, p = 0.72), however, the duration of the diagnostic process before intervention in the center itself dropped significantly in the last decade (from 2.6 years to 1.4 years, p < 0.001). The proportion of successful outcomes for both intracranial (61%, 69%, 59%, p = 0.15) and VNS implantation procedures (56%, 70%, 63%, p = 0.31) remained unchanged among the selected time periods. In the 2011-2020 period, the percentage of extratemporal epilepsies and pathologies other than hippocampal sclerosis markedly increased (from 31% to 51% and 47% to 68%, p < 0.001 and p = 0.02 respectively).

Conclusion: Since 1995, the duration of intractable epilepsy before referral to the Brno Epilepsy Center has not been significantly shortened, there is however a clear increase in the speed of the diagnostic evaluation prior to surgery. Although the outcomes have not changed, the amount of more complex cases being evaluated and treated surgically in the last years has risen sharply. Similar trends have already been observed in other well-established centers worldwide and offer an interesting foray into the future of epilepsy surgery.

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Improving the localization of radiofrequency thermocoagulation using interictal stereo-EEG features in intractable focal epilepsy

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Purpose: The aim of the study was to evaluate particular EEG features in relation to the effectiveness of radiofrequency thermocoagulation (RFTC) within the presumed epileptogenic zone using implanted diagnostic intracerebral electrodes in patients with drug-resistant epilepsy.

Method: As part of the study, we analyzed the data of a group of 21 patients who underwent RFTC since 2017 using stereotactically implanted electrodes. In addition to general clinical characteristics, we studied specific EEG features (high-frequency oscillations (HFO) and entropy) in individual electrode contacts used for RFTC. Finally, we performed a statistical analysis of these EEG features in seizure-free patients compared to patients with persistent epileptic seizures. The follow-up was at least twelve months after RFTC.

Results: The average number of contacts between which RFTC was performed was 6 (range 2-22). After RTFC, two patients were seizure free, 50–90% reduction in seizure frequency was observed in 7 patients and less than 50% in 3 patients. Therefore, the RFTC did not change the frequency of seizures in 9 patients. The frequency and occurrence of HFO was not critical in determining the suitability of thermocoagulation for a particular contact. Nevertheless, regarding an entropy, in the band 1-20 Hz and 250-600 Hz, the relative entropy was significantly higher, in the band 20-250 Hz significantly lower in the contacts used for RFTC in patients with good postoperative outcome.

Conclusion: The presented results of this pilot study are comparable with previously published data. At least a 50% seizure reduction was achieved in 42.9 % of patients (two complete responder). In the future, the analysis of the EEG characteristics of individual electrode contacts could specify the selection of contacts suitable for RFTC.
Partial disconnection surgery as an effective alternative in the treatment of refractory epilepsy: about two cases

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Purpose: Disconnection surgery is a surgical alternative for patients who develop drug-resistant epilepsy. They have been successfully used to treat a wide range of pathologies, including hemimegalencephaly, Sturge-Weber syndrome and porencephalic cyst, among others. When epilepsy is symptomatic of extensive or multilobar lesions, a wide resection surgery would imply greater morbidity and mortality and a worse functional prognosis. Resection surgery may be discarded due to anatomical or functional risks. Partial disconnection techniques in order to limit the recurrence of seizures may offer an option to treat these patients.

Methods: We describe two patients with drug-resistant epilepsy evaluated in our referral center for epilepsy surgery and who underwent partial disconnection surgery after presurgical evaluation.

Results: The first patient is a 13-year-old boy. He was diagnosed with Lennox-Gastaut syndrome with a structural cause secondary to extensive right temporo-occipital focal cortical dysplasia type I. Video EEG monitoring confirmed the existence of epileptic seizures with right temporal focal onset. After presurgical evaluation with epileptic zone located in the right temporal lobe, right temporoparieto-occipital disconnection surgery was performed in 2017. The second patient is a 47 year-old man. He presented with refractory epilepsy and MRI showed left temporo-parieto-occipital nodular heterotopia and ipsilateral mesial temporal sclerosis. VideoEEG monitoring revealed left temporal mesial focal onset seizures. Given the presence of ipsilateral temporobasal venous angioma with increased bleeding risk in case of a typical temporal lobe resection, left temporal disconnection surgery was performed by suprapetrous craniotomy in 2018. Both patients suffered from no complications after surgery without seizure recurrence since then (Engel I).

Conclusions: Partial disconnection surgeries are a safe and effective alternative for selected patients in whom resection surgery is not possible. It is essential to carry out a pre-surgical evaluation to consider all possible options even when direct surgery does not appear to be a treatment option.
Development and validation of the 5-SENSE score to predict focality of the seizure-onset zone as assessed by stereoelectroencephalography

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Purpose: Stereo-electroencephalography (SEEG) has become the gold standard in case of inconclusive non-invasive pre-surgical epilepsy work-up. However, up to 40% of patients are subsequently not offered surgery, as the seizure-onset zone (SOZ) is less focal than expected or cannot be identified. To predict focality of the SOZ in SEEG, we developed and validated a 5-point score (“5-SENSE-score”).

Methods: Monocentric cohort study for score development (Montreal Neurological Institute; 02/2002-10/2018) followed by multicenter validation (05/2002-12/2019) in nine tertiary epilepsy centers. Selection criteria were ≥2 seizures in EEG and availability of complete neuropsychological and neuroimaging datasets. Based on SEEG, patients were grouped as focal and non-focal SOZ. We reviewed demographic, clinical, EEG, neuroimaging, and neuropsychology data. A multiple logistic regression model for developing a score to predict SEEG focality was created and validated in an independent sample.

Results: We analyzed 128 patients (57 women; median age, 31 years [range 13-58]) for score development and 207 patients (97 women, median age 32 years [range 16-70]) for validation. The score comprised the following five predictive variables: focal lesion on Structural MRI (S of SENSE), absence of bilateral independent spikes in scalp EEG (E), localizing Neuropsychological deficit (N), strongly localizing Semiology (S), and regional ictal scalp EEG onset (E). The “5-SENSE-score” had an optimal mean probability cutoff for identifying a focal SOZ of 37.6 [SD=3.5]. Area-under-the-curve, specificity, and sensitivity were 0.83, 76.3% (95% CI: 66.7-85.8), and 83.3% (95% CI: 72.3-94.1). Validation showed 76.0% (95% CI: 67.5-84) specificity and 52.3% sensitivity (95% CI: 43.0-61.5).

Conclusion: High specificity in score development and validation confirms that the “5-SENSE-score” predicts patients where SEEG is unlikely to identify a focal SOZ. It is a simple and useful tool assisting clinicians to reduce unnecessary invasive diagnostic burden on patients and overutilization of limited healthcare resources.
Increase the accuracy of invasive epilepsy treatment by using multimodality brain imaging

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**Purpose:** Despite extensive presurgical work up of epilepsy surgery candidates not all treatment procedures are successful. In case of treatment failure re-analysis can help to identify reasons why procedures failed. Use of multimodality brain imaging tools allows to combine initial and re-analysis results, thus providing a clearer image of the underlying networks aiding the decision-making process towards a more accurate invasive treatment.

**Methods:** Multimodality imaging software was developed to bring the brain imaging and functional neurophysiological datasets acquired during presurgical work up of a patient in the same co-ordinate system. Integration with 3D-mapping of depth electrode or stereo-EEG (SEEG) recordings translates the invasive neurophysiology recordings into the same 3D-space. By combining pre- and post-resection brain images and the results of both SEEG recordings the clinicians were able to evaluate the initial treatment strategy against the re-analysis imaging results what improved the decision making towards reoperation.

**Results:** Shown are the results to illustrate how the integration of non-invasive imaging with 3D-mapping of depth electrode EEG recordings may guide the re-evaluation of candidates for surgical treatment. Compared to the first implantation, showing an epileptogenic network with a single epileptogenic zone, the combination of both datasets showed that following the first SEEG implantation and subsequent resection 1) in case of reoperation the original resection has to be enlarged 2) part of the original network now has to be treated as an independent epileptogenic focus.

**Conclusion:** Applications are designed to provide clinician with an easy-to-use tool for combined visualization of non-invasive and invasive images acquired during the work-up of epilepsy surgery candidates. The software applications made it possible to combine data of all intracranial and non-invasive brain imaging of two different presurgical work ups in the same patient and appears to be a valuable tool in the re-analysis of surgical candidates aimed at reoperation.

Surgical treatment of multifocal extratemporal epilepsy

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**Purpose:** For last decade have been observing the progress in management of multifocal epilepsy. Introduction of modern diagnostic and neurosurgical technologists allow to make resective and disconnecting interventions with minimal damage of brain and high efficiency.

**Methods:** 55 patients with multifocal drug-resistant epilepsy underwent surgical treatment. Among them were 43 (78%) children and 12 (12%) adults. Callosotomy performed in 34 (62%) cases, functional peri-insular hemispherotomy (FH) - in 15 (27%) and 6 (11%) patients underwent multilobar resections (MLR). Postoperative follow-up ranged from 6 months to 11 years (mean – 5.8 years).

**Results:** Multiple epileptiform focuses or diffuse lesion and electric discharges within one hemisphere observed in 21 (38%) cases, bilateral structure lesions - in 30 (55%) cases; MRI-negative epilepsy with bilateral discharges – in 4 (7%) patients.

After surgery 24 (44%) patients became seizures free (Engel Class IA): 13 - after FH, 6 - after MLRand 5 - after callosotomy.

9 (16%) patients had rare short auras or focal seizures (Engel Class II), in 21 (38%) cases seizure frequency reduced less than on 75% or didn’t change significantly. Drop-attacks stopped in 26 of 30 (87%) children who have had them before callosotomy.

Operative complications occurred in 2 (3.6%) children after FH. One child died in three weeks after surgery because of cardiac arrest and developing hypoxic-ischemic encephalopathy. One child (1.8%) developed hydrocephalus needed ventriculoperitoneal shunt placement.

**Conclusion:** Best results were achieved after FH and MLR (90% patients became seizures free), while after callosotomy seizures stopped only in 5 (15%) cases. FH is recommended for unihemispheric epilepsy for children who do not have severe psychiatric disturbances and cognitive decline. While callosotomy is reserved for patients, suffering from severe epilepsy who are not good candidates for resective surgery. The blocking of bilateral epileptogenic activity by callosotomy allows to stop or significantly reduce myoclonic seizures and drop-attacks and improve patient’s quality of life.
Resective epilepsy surgery: experiences from a multidisciplinary epilepsy team in Egypt

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**Purpose:** Resective epilepsy surgery is currently a standard treatment option for focal drug-resistant epilepsy (fDRE). However, surgery is underutilized in limited resources countries (LRC) mainly due to the lack of advanced equipment e.g. invasive monitoring. Nevertheless using available resources to the maximum within a multidisciplinary presurgical evaluation team may present the possibility of resective epilepsy surgery for selected patients with fDRE aiming at achieving seizure freedom and discontinuation of anti seizure medications.

We present our experience in initiating a multidisciplinary team (MDT) for resective epilepsy surgery with limited resources in Egypt and review the postoperative outcomes.

**Methods:** Fifty Patients with fDRE who underwent resective epilepsy surgery within a period of 2 years were reviewed, followed up for at least 12 months, and evaluated for their postoperative outcome. The pre-operative comprehensive assessment included clinical, neurophysiological, neuropsychological, and radiological evaluation, which was performed by a MDT. Intraoperative brain mapping techniques included awake craniotomy and direct stimulation techniques, neurophysiological monitoring, and electrocorticography were carried out. Operative complications, neurological deficits, and extent of resection were evaluated. Engel class I–IV classification was the primary outcome measure of epilepsy surgery.

**Result:** They were 27 male and 23 female patients, with a mean age 16.3 years. Twenty-two patients had temporal lobe pathology, while 28 had extra-temporal. There were no major anesthetic complications. Postoperative immediate neurological deficits occurred in 4 (8%) patients and only one (2%) patient had a permanent deficit. The success rate as Engel class I was achieved in 38 patients (76%). While, 12% and 8% of patients showed Engel class II and III respectively, while two (4%) patients showed no worthwhile improvement as Engel class VI.

**Conclusion:** Despite the limited resource setting, favorable outcomes could be achieved by resective surgery in patients with fDRE after careful presurgical multidisciplinary selection, using the available resources.

Extent of resection in long term epilepsy associated tumours

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**Introduction & Background:** Seizure is a common presentation of gliomas and occur in 50% of all gliomas, and up to 88% in low-grade gliomas. Tumours such as dysembryoplastic neuroepithelial tumours (DNET) and gangliogliomas are commonly associated with epilepsy, and can account for up to 18% of all epilepsy surgery in adults. The extent of surgical resection is the main predictor of post-operative surgical freedom. However, even within patients who undergo a total tumour resection, some continue to have uncontrollable seizures, since the focus of epilepsy may lie in peritumoural tissue.

**Methods:** This is a retrospective analysis of patients with temporal low grade gliomas including ganagliogliomas DNET, and PXA treated at Western University in the last 20 years. The aim of this study is to determine the effect of the extent of resection in temporal low grade gliomas in adults, specifically gangliogliomas, dysembryoplastic neuroepithelial tumours (DNET), and pleomorphic xanthoastrocytomas (PXA), on post-operative seizure control. The main comparison is the extent of surgical resection divided into four groups: lesionectomy, lesionectomy + mesial structure resection, anterior temporal lobectomy, or anterior temporal lobectomy + mesial structures resection.

**Results:** Primary outcomes included pre and post-operative seizure frequency to calculate the Engle surgical outcome9. Secondary outcomes include time to first seizure, tumour recurrence, survival, and post-operative cognitive side effects.

**Conclusion:** This study aims to define a resection strategy for optimal seizure control in patients with temporal low grade lesions. Due to the effect of temporal lobe gliomas on peritumoural brain, extended surgical resection, i.e. lesionectomy, anterior temporal lobectomy, and amygdalohippocampectomy produces the best long term seizure control in patients with temporal low grade tumours. Additionally, prolonging time between diagnosis and surgery can correlate negatively with post-operative seizure control, especially in patients who had not undergone an extended resection
Outcome of vagal nerve stimulation for intractable epilepsy: the study from Korean National Hospital Registry

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Purpose: For fifteen years since vagal nerve stimulation (VNS) is supported by national health insurance in 2005, 999 cases of VNS implantation were performed in Korea. This study aimed to assess the outcome and prognostic factors of VNS for intractable epilepsy.

Method: We included the people with epilepsy who underwent VNS and had been treated in national hospitals between January 2005 and December 2018. 189 patients from 10 hospitals were recruited. Baseline clinical characteristics, seizure frequency and number of anti-seizure medication (ASM) measured every three months for one year before and after surgery, and surgical complications were collected from medical records. Health resource utilization for one year before and after surgery was assessed from health insurance data.

Results: In comparison between pre- and post-surgery one year, 50% or more seizure reduction was achieved in 53 (28.0%) patients, while seizure frequency increased twice or more in 8 (4.2%) patients. Seizure-free for one year or more was achieved in 11 (5.8%) patients. Seizure frequency significantly decreased in 50 (26.5%) and increased in 7 (3.7%) (Interrupted time series analysis). Number of ASM prescribed one year after surgery was median, 5 [IQR 4 to 6], same as just before surgery. Number of admission or ER visit associated with status epilepticus were median 1.0 [IQR 1.0 to 3.5] before surgery and median 1.0 [IQR 1.0 to 2.8] after surgery. Pre and post-surgery epilepsy related medical cost was median 3,330 dollars and 3,220 dollars without significant difference. Factors associated with favorable outcome were not identified except focal spike with secondary bilateral synchrony in electroencephalography (odds ratio=2.3 [95% confidence interval 1.1 to 4.9]).

Conclusion: The efficacy of VNS for intractable epilepsy varied depending on individuals. However, VNS was significantly beneficial in some patients. Focal spike with secondary bilateral synchrony is a factor predicting good response to VNS.

Machine learning algorithm for surgical treatment outcome prediction in pediatric patients with epilepsy

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The use of automated tool predicting outcomes of epilepsy surgery are becoming more used. We implemented, trained and tested a predictive model based on Machine Learning (ML) algorithm predicting surgical outcome in a pediatric cohort. We extract and analyze different type of complex and non-linear features of SEEG signals. This technique is evaluated with different performance measures: accuracy, sensitivity, and precision for each surgical outcome (seizure free vs non-seizure free).

49 pediatric patients underwent SEEG implantation in our institute between 2009 and 2019 with a minimum post-surgical follow-up of 2 years. Matlab software was used to design and train the network in a feedforward backpropagation. Power Spectrum, Coherence, Bi-spectrum, Entropy, Lyapunov and Hjorth features of SEEG data, (128 channels), were used to quantify the EEG. Nine architectures of Artificial Neural Network (ANNs), with different number of Hidden Layers (HL, 1-3) and Neurons (N, max 30), were used to predict postoperative outcome in the 8 patients. We used two combinations of features: all predictors vs those selected with statistical regression method. To evaluate system accuracy, each postoperative outcome predicted values were compared with actual outcomes. The SEEG parameters and the ANN with 2 HL and 15 N in the first HL predicted two class of surgical outcomes with a mean accuracy of 70%. The prediction accuracy decreased to 62% when only statistically significance SEEG features were used. Predictor statistical analysis used to evaluate the most important predictors of the outcome didn’t show improvement of result.

As a complex non-linear mathematical model, our ANN system is an interconnected data mining tool which prospectively analyzes relationships between electrophysiological variables. These results demonstrate an efficient utilization of ML to predict clinical outcomes providing an improvement in predictive performance over classical statistical methods. Our findings suggest that this tool may be easily used during a presurgical consultation.
Seizure-free outcome and safety of repeated epilepsy surgery for persistent or recurrent seizures

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Purpose: Reoperation may be an option for selected patients with unsatisfactory seizure control after the first epilepsy surgery, yet reports in the literature are limited. We describe seizure-free outcome and safety of repeated epilepsy surgery in our tertiary referral center.

Method: Thirty-eight patients with focal refractory epilepsy, who underwent repeated epilepsy surgeries and had a minimum follow-up time after reoperation of six months, were included. Systematic reevaluation including MRI and non-invasive (n=38) and invasive video-EEG-monitoring (n=25, 66%) was performed. FDG-PET was acquired in 20 patients (53%), ictal SPECT in 17 (45%). Multimodal three-dimensional resection maps were created for individual patients to allow personalized reoperation. Awake craniotomy with intraoperative language monitoring was performed in ten patients (26%).

Results: Median time from first operation to reoperation was 74 months (range: 5-324). Median age at reoperation was 35 years (range: 1-74), median follow-up was 32 months (range: 7-142). Repeated MRI after the first epilepsy surgery showed an epileptogenic lesion in 24 patients (63%). The reoperation was temporal in 18 patients (47%), extra-temporal in nine (24%), and multilobar in eleven (29%). The reoperation was left-hemispheric in 24 patients (63%), close to eloquent cortex in 19 (50%), and distant from the initial resection in nine (24%). Following reoperation, 27 patients (71%) became seizure-free (Engel class I), while eleven (29%) continued having seizures. Neither demographic nor clinical factors were associated with seizure-free outcome. Perioperative complications occurred in four patients (11%), with no fatalities.

Conclusion: Reoperation for refractory focal epilepsy is an effective and safe option in patients with persistent or recurrent seizures after initial epilepsy surgery. A thorough presurgical reevaluation is essential for favorable outcome.

The long-term distribution of seizures in a mouse model of focal cortical dysplasia type II

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Purpose: Studies in animal models of epilepsy and humans with epilepsy demonstrated long-term fluctuations or cyclicity in seizure risk. It is now believed that long-term rhythms represent a crucial component of ictogenesis. The goal of this study was to explore the long-term distribution of seizures in a model of focal cortical dysplasia (FCD).

Method: FCD was induced using in utero electroporation of plasmid containing mTOR with p.Leu2427Pro mutation. Animals were implanted with epidural electrodes and video-EEG monitored for >2 weeks. Recorded data were analyzed visually. Seizure severity was scored according to the modified Racine scale. A seizure cluster was defined as a group of >5 seizures followed by a seizure-free period.

Results: All animals (n=5) displayed long-term fluctuations in seizure probability. Three exhibited seizure accumulation into the clusters. One mouse exhibited five clusters of 5-7 seizures with an inter-seizure interval of 6.4±0.6 minutes. The clusters were separated by 5 hours to 5 days. The other two mice had more extended clusters containing 12±4 seizures with an inter-seizure interval of 4.4±0.9 hours and inter-cluster periods of 1 to 4 days. The seizure duration of 51±2 s was consistent across animals. We discovered gradual prolongation of the seizure duration and progressively increasing severity of the seizures along with the cluster progression (p=0.0078, signed-rank test).

Conclusion: Our data demonstrate that a murine model of FCD is associated with seizure clustering similarly to other epilepsy models and human patients. We described the internal dynamics of the clusters, namely the gradual increase of seizure duration and severity. These data could contribute to a better understanding of seizure predisposition.

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Focal neuronal lipofuscinosis causing medically refractory frontal lobe epilepsy: paediatric case report of an ultrarare histology in epilepsy surgery

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Purpose: There are only 7 reported cases in literature of focal neuronal lipofuscinosis (FNL) in epilepsy surgery specimens- all affecting frontal lobe². We describe the 2nd paediatric case overall. This case is the only one with clinical exome sequencing (CES) done preoperatively- reported normal.

Method: We report clinical and 2 stage presurgical evaluation details of a 12 year old, right handed girl with medically refractory epilepsy. Focal seizures started at 10 years of age. The semiology was stereotypical- aura of heaviness in right upper limb, behavioural arrest, head/trunk version to right and an unusual smile with rare right upper limb clonic jerking and/or a fall. No postictal upper limb weakness noted. Past medical history was insignificant. Her grandfather had epilepsy. 1st stage presurgical evaluation was strongly suggestive of left prefrontal localisation (dominant lobe) but was MRI negative. Stereo EEG implantation in left frontal lobe showed distinct epileptogenic abnormality over the left middle frontal gyrus (LMFG).

Results: Tailored resection of LMFG was done- guided by intraoperative monitoring and neuronavigation. Patient developed transient expressive aphasia. She is now seizure free for 2 years postoperatively. Histopathology and immunohistochemistry of surgical specimen showed dysmorphic neurons with accumulation of lipofuschin.

Conclusion: FNL is an ultra rare, histologically identified etiology of medically refractory frontal lobe epilepsy. Lipofuschin is proposed to be result of autophagy in dysfunctional neurons- mediated by genes which control autophagy and vesicle trafficking¹. Cases in literature experienced seizures for mean of 16.6 years (range 8-25) preceding surgery. The distinct features of shorter duration of preceding seizures (2 years in this child) and normal CES have the potential to further the understanding of pathogenesis of FNL.

References:

Epileptogenic low grade gliomas: treatment results

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Purpose: Seizures are the most common presenting symptom of newly diagnosed low-grade gliomas (LGG) and significantly impair quality of life. Achieving freedom from seizures is one of the main goals of surgical treatment.

Methods: A retrospective analysis of 135 surgical interventions on epileptogenic LGG that were performed at the Municipal Non-profit Enterprise “Regional Clinic Center Of Neurosurgery And Neurology” Transcarpathian Regional Council during the last 9 years (January 2013 to January 2022). Patients with post-operative follow-up more than one year were assessed according to Engel scale.

Results: Seizures were the presenting symptom in 71% of patients with LGG. Astrocytomas were the most frequent histological type of LGG (74%). There were 75% Engel class I, 20% in class II, 2.5% in class III, 2.5% in class IV patients. Engel class I was in 71% of patients with total tumor removal and in 65% of patients with subtotal/partial removal. No significant differences in seizure outcome were observed between astrocytic versus oligodendrogial tumors.

Conclusions: Seizure control is one of the most important considerations in planning surgery for low-grade brain tumors. Surgical treatment, particularly gross tumor resection, contributes strongly to seizure freedom.
Mood disturbances before and after resective surgery in pediatric epilepsy: preliminary findings

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Purpose: Depression and anxiety are two of the most common psychiatric manifestations in children with intractable epilepsy. ILAE standards and indications stated that presurgical evaluating protocols should include formal measures of mood assessment. In our study, we have evaluated pre-post mood levels in a sample of children undergoing resective surgery.

Method: 126 patients undergoing resective surgery between 2019-2021 at the Bambino Gesù Children Hospital were assessed during scheduled evaluation and counseling clinics. Of these, only 66 were suitable for mood assessment due to age (≥ 11 years old), then 29 patients were excluded because of missing pre-operative data or non-assessable (QI< 75) and 13 didn’t complete follow-up examination. We screened mood disturbances by using the Patient Health Questionnaire (PHQ-9) and the Generalized Anxiety Disorders (GAD-7) Questionnaires. We performed pre-surgical examination (T0) and post-operative evaluation (T1) after approximately 1 year and/or according to tailored clinical needs.

Results: We found moderate-to-elevate percentages of anxiety depressive symptoms both before and after surgery in our sample (n= 24, M:14, F:10; MAge: 16.5 yrs). In detail: depressive symptoms (mild to severe) were present in 37.5% of the sample both in T0 and T1, while anxious disorders (mild to severe) were present in 45.8% of the sample in T0 and in 41.7% in T1. Comorbidity was present in 25% of the sample in T0 and in 33.33% in T1. Despite the anxious symptomatology decreased over time, it was not statistically significant (paired t-test, P = 0.528).

Conclusions: Preliminary data showed 1-year mood stability in a sample of children with intractable epilepsy after resective surgery. Referring to the literature evidence of high risk for mood disorders, this result may represent an encouraging outcome. Proactive management of surgical resection in pediatric epilepsy should be promoted and complemented with standardized screening tools also for psychiatric comorbidities and PTSD.

Hemispherotomy is the most efficient surgical procedure for drug-resistant hemispheric epilepsy in children

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Purpose: The aim of our study is to present the first series of children with drug-resistant hemispheric epilepsy treated with hemispherotomy in Bulgaria. We reviewed the indications and results from this aggressive neurosurgical operation.

Method: Our retrospectively analyzed cohort includes eight consecutive children operated on during 10-year period (2011-2020). We have used lateral (peri-insular) technique in 7 children, and vertical (parasagittal) technique in one child.

Results: The most frequent hemispheric lesion in our series was a large porencephalic cyst associated with gliosis due to hypoxic-ischemic injury (4 children). The other hemispheric pathologies were Sturge-Weber syndrome (2 children), Rasmussen encephalitis (1 child) and hemimegalencephaly (1 child). Complete seizure control was achieved in all 8 children. Anti-seizure medication was stopped in 4 children. There was no worsening of the preoperative neurological deficit. The only complication in a child with Sturge-Weber syndrome was a postoperative communicating hydrocephalus after peri-insular hemispherotomy, and was successfully treated with lumbo-peritoneal anastomosis.

Conclusion: Hemispherotomies are the most successful operations for drug-resistant hemispheric epilepsies in children. Nowadays, after 15 years of experience, the epilepsy surgery in Bulgaria includes the whole spectrum of surgical interventions - from minimally invasive procedures such as vagus nerve stimulation to the most complex and extensive surgeries such as hemispherotomy.
Introducing of prospective quality of life assessment in pediatric epilepsy surgery patients: a pilot study

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Purpose: This study aimed to introduce a systematic monitoring of the health related quality of life (HRQoL) in children undergoing resective epilepsy surgery in Motol Epilepsy Center, Prague. In long term we aim to analyze effects of epilepsy surgery on various aspects of HRQoL.

Method: We have recruited children with focal intractable epilepsy evaluated in Motol Epilepsy Center as potential candidates of of resective or disconnective epilepsy surgery. The recruitment started in May 2019. The inclusion criteria were: 1) age between 11 and 18 years, 2) IQ above 70 points. To evaluate the HRQOL we used QOLIE-AD-48 (Health-Related Quality of Life Measure for Children with Epilepsy). The Czech version of QOLIE-AD-48 consisting of six domains (Epilepsy impact, Memory, Physical functioning, Stigma, School behavior, Health perceptions) was standardized in our previous study. The questionnaire was administered to all patients during the diagnostic work-up and in operated patients 6, respectively 12 months after the surgery. For preliminary results we analyzed data available until February 2022.

Results: We obtained presurgical evaluation of quality of life from 29 children. Surgery was not indicated in 4 cases, in 2 cases the diagnostic process was incomplete and in 4 the final follow-up was less than 6 months after surgery. Retests were available in 19 operated patients (in 17 cases after 6 months, in 16 cases after 12 months, in 11 cases both). We observed significant improvement in Health perception domain (p=0.003, resp. p<0.001) and Stigma domain (p=0.049, p=0.013), both 6 and 12 months after epilepsy surgery. In Epilepsy impact domain we observed significant improvement only after 6 months after surgery (p=0.030).

Conclusion: Systematic monitoring enables advanced analysis of impact of epilepsy surgery on quality of life in pediatric patients.

Fever during depth electrode prolonged extra-operatory recordings: how common is it and what does it mean?

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Purpose: Depth electrodes are a valuable tool in the investigation of focal refractory epilepsies with infrequent complications. Non-infectious fever has been reported in context of intracranial electrode implantation, however, its true incidence and significant have not yet been explored in detail; we purposed to address these issues in this work.

Methods: Retrospective observational study on patients that underwent intracranial EEG recordings with depth electrodes at a Portuguese epilepsy referral centre (November 2017 to December 2021). Data collection included sociodemographic and epilepsy characteristics, electrode trajectories, paraclinical records and three daily tympanic temperature (TT) readings. Patients with simultaneous subdural electrodes were excluded. Fever was defined as TT≥38ºC and subfebrile as TT 37.5-37.9ºC.

Results: Thirty-one subjects were included [median age 42-yo (IQR 30-53), 17 female (55%)]. Most patients had temporal mesial (n=9, 29%) or multilobar (n=9, 29%) epilepsy. The median maximal TT was 37.6ºC (37.4-38.1). Ten individuals developed fever (32%) and 13 were subfebrile (42%); within a median time from implantation of 1 day (IQR 1-3). Twenty-five patients (81%) had at least one intraventricular electrode contact; such subjects had a higher risk of fever (10/25 vs. 0/6; p=0,141), without correlation with the number of intraventricular contacts (p=0.608). Fever was not related to the presence of haemorrhage (p=0.296), oedema (p>.990) or air (p>.990) on brain-CT. There were five clinically relevant events: subdural hematoma, cystitis, intestinal pseudo-obstruction, and thalamic infarction (n=1 each); these were not associated with fever development (p=0,577). There were no CNS infections nor permanent neurological deficits.

Conclusion: In our experience, up to a third of patients performing intracranial recordings with depth electrodes had fever, and none had a documented infection. The risk of fever was higher if there were intraventricular electrode contacts. Fever should always alert to the risk of infectious complications, but in this setting it is often benign and self-limited.
Defining spike propagation onset with electric source imaging predicts surgical outcome in children with drug-resistant epilepsy

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**Purpose:** Spikes are the leading epilepsy biomarkers in intracranial EEG (iEEG), but they suffer from low specificity in identifying the epileptogenic zone, the brain area that is indispensable for the generation of seizures. Previous studies have shown that spikes propagate in time across large brain areas and that the onset of this propagation is more epileptogenic than areas of spread. Yet, the iEEG may miss the complete spatiotemporal evolution of this propagation due to its limited spatial resolution. Here, we use electric source imaging to delineate the spatiotemporal propagation of spikes and evaluate its predictive value in epilepsy surgery.

**Method:** We analyzed iEEG data from 30 children (16 with Engel 1) with DRE who underwent resective surgery with available surgical outcome at least one year after surgery. For each patient, we reconstructed the spike propagation evolution via an in-house algorithm based on the dynamic Statistical Parametric Mapping inverse solution. On the patient’s MRI volume, we then defined onset and spread zone, and quantified the overlap of these regions with resection volume (ORES), and their mean distance from resection (dRES).

**Results:** We observed spike propagation in all patients with a median duration of 93 ms [IQR: 29-180 ms]. The onset was more focal compared to the spread zone ($p=0.006; 4.6$ vs. $17.4$ cm$^3$). Higher ORES and shorter dRES were seen for the onset than the spread in good outcome patients (ORES: $p=0.003, 97$ vs. $61$%; dRES: $p<0.001, 4.6$ vs $9.8$ mm). Resecting >90% of the onset but not of the spread area was able to predict the postsurgical outcome (onset: $p<0.001$, PPV=93%, NPV=61%; spread: $p=0.11$, PPV=88%, NPV=49%).

**Conclusion:** Mapping spike propagation onset with electric source imaging allows prediction of surgical outcome in children with DRE. Such a biomarker’s development may result in more accurate and less time-demanding presurgical evaluation.

Seizure outcomes in persons with autism spectrum disorder undergoing epilepsy surgery: a systematic review

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**Purpose:** Autism spectrum disorder (ASD) and epilepsy commonly co-occur. Resective and non-resective surgeries can be effective treatments for patients with drug resistant epilepsy. However, past research in patients with ASD and epilepsy has yielded mixed results in regard to seizure outcomes following epilepsy surgery. We performed a systematic review focused on outcomes of epilepsy surgery in patients with ASD.

**Methods:** We adhered to the PRISMA standards. Using relevant search terms, MEDLINE, Embase, and PsycINFO were queried from inception to December 2021. Studies were included if they reported seizure frequency following epilepsy surgery in persons with ASD.

**Results:** 593 abstracts were identified, out of which 78 were selected for full text review. Thirty-seven studies reporting on 292 patients were included. 126 patients underwent resective surgery, 146 underwent neuromodulation (139 VNS, 6 RNS, 1 DBS), and 19 underwent other palliative procedures (15 corpus callosotomy, 4 multiple subpial transection). Outcomes were stratified into four categories based on a combination of Engel classification and percentage seizure reduction at latest follow-up. The distribution of seizure outcomes for all procedures was as follows: $27.74%$ Engel I or seizure free, $17.12%$ Engel II or $>75%$ seizure reduction, $21.23%$ Engel III or $50-74%$ seizure reduction, $33.56%$ Engel IV or $<50%$ seizure reduction. Resections resulted in more favorable outcomes compared to VNS neuromodulation ($50.79%$ Engel I vs. $7.91%$ Engel I, $p = 0.028$).

**Conclusions:** Based on past work, there is potential for properly selected patients with ASD and epilepsy to experience a significant reduction in seizure frequency or seizure freedom following resective and non-resective epilepsy surgery. While there is a need for more large prospective studies, our review suggests that ASD patients may benefit from surgical treatment.
Five nomograms and a scale to predict the outcome of epilepsy surgery – an external validation and head-to-head comparison study

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Purpose: The aim of current study was to externally validate and to compare four different epilepsy surgery outcome prediction systems, three nomograms and the Epilepsy Surgery Grading Scale (ESGS).

Methods: 211 patients with therapy-resistant focal epilepsy, undergoing surgical evaluation were retrospectively enrolled (presurgical group). Relevant data was extracted from the patients’ charts. Individual predictions were calculated using the nomograms, and patients were classified into the three scales according to the ESGS. Progression to surgery, and postsurgical seizure freedom and Engel score were assessed.

Results: 139 patients underwent epilepsy surgery following the evaluation. The models for complete seizures freedom had a c-statistics of 0.56 at two years with clinical features only, 0.57 including the scalp EEG findings, and 0.62 at five years. For an Engel score of 1 the c-statistics was 0.60 and 0.63 at two and five years, respectively. With ESGS, we observed significant difference between grades 1-2, and 1-3 (p < 0.001 and p < 0.001 respectively), and a trend to significance between grades 2-3 (p = 0.064) in the presurgical group. In the surgical group there was a significant difference between grade 1-2 (p = 0.007) but we did not observe a statistically significant difference between grades 1-3, and 2-3. When, in contrary to the original nomogram, limiting the presence of focal-to-bilateral tonic-clonic seizures (FBTCS) to the one year before the surgery, we acquired generally better fitting calibration curves and higher c-statistics (mean improvement was 0.0346, highest improvement 0.116).

Conclusion: Our findings present similar concordance statistics for the nomograms as the original publications, improved by limiting FBTCS to the one last year before surgery. We present the first external validation for the nomogram, which includes both clinical features and scalp EEG findings in the evaluation (the improvement is 0.01). We confirm the usefulness of the ESGS.

Genetics

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Predictive indices for the efficacy of genetic panels in pediatric epilepsy

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Purpose: Genetic panels are frequently used in the diagnostic workup of epilepsy patients. However, their yield of definitive diagnosis is relatively low, and the results can include variants of uncertain significance (VUS) necessitating follow-up tests. Our aim was to identify the clinical characteristics associated with high likelihood of reaching a definitive genetic diagnosis by these panels in order to increase their efficacy.

Methods: We performed a retrospective cohort study, of 201 epilepsy patients in the Safra Children's Hospital at Sheba Medical Center, between June 2018 and August 2021, for which the „Invitae” epilepsy genetic panel test was performed. The clinical characteristics evaluated for their predictive value were: epilepsy type and severity, seizures-onset age, history of first-degree relative with seizures or epilepsy and coexistence of dysmorphism or autism/intellectual disability (ID). Comparison between patients in whom a definitive genetic diagnosis was made to those in which it was not, with regards to these clinical variables, was performed using chi-squared test. Logistic regression was applied to create a multivariate model.

Results: A definitive genetic diagnosis was found in 33/201 (16.4%) patients for whom the panel was performed, among those, SCN1A was the most common gene (5/33, 15%) and the median seizures-onset age 9 was months. The clinical characteristics that were significantly associated with obtaining a definitive genetic diagnosis were: existence of dysmorphism (13/33, 39.3%, p=0.0001), febrile seizures or generalized epilepsy febrile seizures plus (10/26, 38.4%, p=0.003) and seizure-onset<12 months (17/57, 29.8%, p=0.0001). Co.existence of autism/ID reached near-significance (19/87, 21.8%, p=0.07).

Conclusions: The efficiency of genetic epilepsy panels used without stringent clinical criteria is relatively low. We suggest it can be raised considerably by recommending them only under certain clinical indications. This could reduce the burden on families and health-systems due to VUS and might lead to their subsidization under specific phenotypic labels.
Outcomes in people with developmental and epileptic encephalopathies surviving into adulthood: what happens?

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Purpose: Developmental and epileptic encephalopathies (DEE) are amongst the most severe epilepsy syndromes. Typically, DEEs present in childhood, with evolving refractory seizures, developmental delay, and multiple comorbidities. Despite their high premature mortality, there are many individuals who survive into adulthood. Nevertheless, long-term evolution of DEEs in adults remains largely unknown. Here we explore the long-term outcome of adults with DEEs with respect to seizure control, comorbidities and functional outcomes. Additionally, we investigate which of the DEEs can still be considered epileptic encephalopathies, indicating the potential influence that this may have on treatment strategies.

Method: Adults with DEE diagnosis at some point in their history were included in this retrospective single-centre observational study. Molecular genetic results were obtained through gene panels, whole exome sequencing (WES) and whole genome sequencing (WGS) from clinical and research environments, including the UK 100,000 Genomes Project. Research results were confirmed by accredited clinical genetics laboratories. Genetic diagnosis was established using accepted classification criteria, following discussion at multidisciplinary meetings. Medical records were reviewed for information on disease progression in several domains.

Results: A total of 110 adults with genetic diagnosis of DEE were included; mean age 33 years (range:17-71), including some of the oldest described so far for specific genes. Overall, 36 genes were involved. Progressive decline in motor skills (n=42, 38.1%) and swallowing function (n=26, 23.6%) was most commonly seen, with cognitive (n=8, 7.3%) and behavioural worsening (n=2, 1.8%), being less frequent. Improvement in cognitive function was seen in three patients (2.7%) following improved seizure control. In 48/80 (60%) cases with available electroencephalographic data, there was evidence of encephalopathy.

Conclusions: These preliminary results show that there is progression in several domains over time, with ongoing encephalopathy evident in the majority of the known DEEs. In some, optimising seizure control can lead to improved outcomes.
Comparison of variant effects in SCN-gene paralogs predict function across sodium channelopathies

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Purpose: Variants in the voltage-gated sodium channel family (SCNs) lead to epilepsy, neurodevelopmental disorders, cardiac arrhythmias, skeletal muscle channelopathies and peripheral neuropathies. Variant effect can guide therapeutic strategy but requires laborious electrophysiological study. Given the evolutionarily conserved nature of sodium channel genes, we investigated whether similarities in biophysical properties between different SCN-gene paralogs can predict function and inform precision treatment.

Methods: We performed a systematic literature search identifying functionally assessed variants within all genes in the SCN-family until 28 April 2021. We included missense variants that had been electrophysiologically characterised in whole-cell patch-clamp recordings. We performed an alignment of linear protein sequences of all sodium channel genes and correlated variants by their overall functional effect.

Results: Of 951 identified records, 437 variants met our inclusion criteria. 141 variants were epilepsy-associated (SCN1/2/3/8A), 79 had a neuromuscular phenotype (SCN4/9/10/11A), 149 had a cardiac phenotype (SCN5/10A) and 68 (16%) were considered benign. We detected 38 pairs of missense variants with an identical disease-associated variant in a different SCN-gene. Missense variants in each pair (35/38 = 92%) produced similar functional effects. Pathogenic missense variants clustered in specific functional domains, whereas population variants were more frequent across non conserved domains (odds ratio = 16.4; 95% CI = 9.9 to 29.1; P<0.001). Pore-loop regions were frequently associated with loss-of-function variants, inactivation sites were associated with gain-of-function (odds ratio = 42.05, 95% CI = 14.5 to 122.4; P<0.001) and variants in voltage-sensing regions comprised a range of gain- and loss-of-function effects.

Conclusion: Our findings suggest that functional characterisation of variants in one SCN-gene can predict channel function across different SCN-genes where experimental data are not available. The collected data represent the first GoF versus LoF topological map of SCN proteins indicating shared patterns of biophysical effects aiding variant analysis and guiding precision therapy.
Purpose: We aimed to expand the genotypic and phenotypic spectrum of pathogenic variants in the GATOR1 complex genes: DEPDC5, NPRL2 and NPRL3.

Method: We analysed the phenotypes and genotypes of 99 new patients with GATOR1 pathogenic variants, together with additional phenotypic information for 89 previously published patients, recruited through international collaborative networks. Variants included were protein-truncating or (likely) pathogenic according to in silico prediction tools.

Results: 188 patients were recruited with pathogenic variants in DEPDC5 (n=145), NPRL2 (n=14) and NPRL3 (n=29), including 43 novel variants. Focal epilepsy occurred in 166/188 (88%) patients. Sleep-related hypermotor epilepsy occurred in 49/188 (26%), frontal lobe epilepsy in 33/188 (18%) and temporal lobe epilepsy in 30/188 (16%). Multifocal epilepsy occurred in 6/188 (3%). Age of seizure onset ranged from day of birth to 64 years (median 4 years). 72/188 (38%) patients were seizure-free, while 83/188 (44%) had at least monthly seizures. Developmental delay/intellectual disability was present in 46/188 (24%), preceding seizure onset in 7 patients. Regression occurred in 14/188 (7%). Psychiatric comorbidities occurred in 41/188 (22%), including autism spectrum disorder in 19/188 (10%). MRI showed focal cortical dysplasia in 24/188 (13%) of patients and other types of cortical malformations in 15/188 (8%). Of the four most frequently used anti-seizure medications, discontinuation rates were lower for carbamazepine (57/129, 44%) and lamotrigine (23/55, 42%) than for valproic acid (64/99, 65%) and levetiracetam (48/76, 63%).

Conclusion: Epilepsies due to mutations in the genes encoding the GATOR1 complex typically present as unifocal epilepsy, predominantly arising in the frontal and temporal lobes, but multifocal epilepsy is also found. Psychiatric comorbidities and developmental delay are common. Developmental delay may be present before seizure onset. Early recognition of malformations is critical as surgical treatment may be an option for patients with drug-resistant epilepsy.
Mutation landscape in 155 children with developmental and epileptic encephalopathies

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Purpose: Developmental and Epileptic Encephalopathies (DEEs) describe children with early-onset epilepsy and global delay attributable to both the underlying cause and/or uncontrolled epileptic activity. The diagnostic yield of genetic investigations in DEEs is high, and depends on phenotype homogeneity of the selected patient, sequence and depth of genetic investigations, technical skills, and expertise in variant interpretation and genetic data reanalysis. We analyzed a retrospective cohort of children with DEE recruited over a one-year period at three highly-specialized paediatric neurology centres with similar genetic investigation practices, following a clinical selection process.

Method: Clinical information was retrieved from local databases and patient files over a 15-month period. Inclusion criteria were: <18 years at disease onset, severely impaired neurodevelopment, difficult-to-treat epilepsy. Children with brain malformations explaining epilepsy were excluded. All patients from one centre were blindly cross-selected by the two other centres using exclusively clinical criteria. Whole-exome sequencing, bioinformatic analysis of selected gene panels and/or array CGH were performed in all. Variants were classified according to the 2015 ACMG criteria.

Results: 155 patients were included. A causal variant was found in 103 (66.5%), with comparable results from the recruitment 3 sites. The diagnostic yield was highest (79/110 children, 71.8%) when seizures had started < 1 year, and decreased with age (17/30 children aged 1-3 years, 56.7%; 7/15 children > 3 years, 46.7%). Eight genes accounted for 58.9% of diagnostics in the entire group, and for 88% in children < 1 year.

Conclusion: The strict criteria used for patient selection, and the cross-validation process between centres allowed high phenotypic homogeneity. To our knowledge, our diagnostic yield is the highest reported so far in a cohort of children with DEE. Our results suggest that genetic testing should be particularly considered in children whose symptoms start before 3 years.

Genetic polymorphisms of dopamine receptors are not related with depression in temporal lobe epilepsy caused by hippocampal sclerosis

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Depression is the most prevalent psychiatric disorder in patients with temporal lobe epilepsy caused by hippocampal sclerosis (TLE-HS). Mechanisms of epilepsy and depression include abnormalities in the dopamine (DA) pathway. We aimed to determine the possible association between the most expressed D2-like receptors in the limbic system's polymorphisms and major depressive disorder (MDD) in patients with TLE-HS. Our secondary aim was to evaluate the possible association between these variants and seizure susceptibility in TLE-HS.

We assessed 119 patients with TLE-HS, with and without psychiatric disorders (PD), 146 patients with MDD, and 113 controls. We excluded patients with other epileptic syndromes, dual pathology, or absence of a structural lesion. We genotyped the DRD2 rs1800497 and D4 rs1800955 by RT-PCR and D4 VNTR by PCR amplification using the capillary electrophoresis system. Categorical variables were compared between groups by the two-tailed chi-square test and Fisher's exact test, whereas numerical variables were analyzed by the Kruskal-Wallis test. Type I error was set at 5%, and adjustment for multiple testing was carried out by Holm-Bonferroni Sequential Correction.

Results:
rs1800497: There was no difference between the TLE-HS and control (p=1.000); TLE-HS and MDD group (p=0.342);
MDD and control (p=1.000) and TLE-HS with MDD and MDD without epilepsy (p=1.000).
rs1800955: There was no difference between the TLE-HS and control (p=1.000); TLE-HS and MDD group (p=0.618);
MDD and control (p=0.618) and TLE-HS with MDD and MDD without epilepsy (p=1.000).
D4 VNTR: There was no difference between the TLE-HS and control (p=1.000); TLE-HS and MDD group (p=1.000);
MDD and control (p=1.000) and TLE-HS with MDD and MDD without epilepsy (p=1.000).
The polymorphisms related to DA transmission were not related to the susceptibility to develop TLE-HS or the presence of MDD in patients with TLE-HS. Further studies with larger series are necessary to corroborate these findings.
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Diagnostic yield of targeted monogenic epilepsies genes panel sequencing: report of our experience in Lyon, France

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Purpose: Epilepsies are frequent as a group of pathologies since they affect about 1% of the population, mostly children. In addition to a broad phenotypic spectrum, the genetic heterogeneity is considerable in these pathologies, with a large number of genes identified these last years thanks to next generation sequencing development. We aimed to assess the utility of targeted gene panel testing of known genes involved in monogenic epilepsies.

Methods: We retrospectively analyzed the diagnostic yield of targeted gene panel sequencing of 115 genes in patients with epilepsy of unknown etiology, familial or sporadic, and whose clinical and electrophysiological characteristics were extensively reviewed, including therapeutic efficacy.

Results: In our cohort of 558 patients (286 females and 272 males), from 50 French centers, with a median age of 6 years and 5 months, the overall diagnostic yield was 32.3% (180/558). We identified 186 disease-causing variants, including 10 small CNVs (8 deletions and 2 duplications), and 4 validated mosaic variants. Most of these variants occurred de novo (72/104). Genetic heterogeneity was indeed significant (58 genes involved in our cohort). However, a few genes were more recurrently involved, such as KCNQ2 (n=16), GRIN2A (n=12), SCN1A (n=12), ATP1A3 (n=11), KCNT1 (n=10), and PRRT2 (n=10). Early epilepsies led to a significantly higher diagnostic rate, reaching 41.4% in patients whose epilepsies began before 3 months of age (63/152). The diagnostic yield was particularly high for epileptic encephalopathies, including CSWS encephalopathies, and for Doose and Dravet syndromes. Five prenatal diagnoses were performed in our center after these molecular diagnoses, and several patients benefited from effective therapeutic adaptations.

Conclusions: Targeted gene panel sequencing is a useful diagnostic tool for epileptologists and epileptic patients. Molecular diagnosis is essential for genetic counseling, and the prognosis of these patients may be improved by earlier selection of appropriate treatments based the molecular results.

Progressive myoclonus epilepsy: a new variant mutation in the neuroserpin gene

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Purpose: Report a new variant of the neuroserpin gen causing progressive myoclonus epilepsy (PME)

Method: A 39-year-old Spanish female who presented 8 years prior with generalized tonic-clonic seizures. Neuroimaging and electroencephalographic monitoring were normal in the beginning. Seizures persisted despite treatment with Levetiracetam, so Lamotrigin was initiated. Generalized seizures were controlled then, but she developed myoclonic jerks, reason why Lamotrigine was suspended. She was partially controlled with a drug combination. However, she persisted with frequent myoclonic jerks (specially induced by movement and sensitive stimulus), myoclonic tremor, instability with frequent falls and cognitive impairment, that progressively worsened through the years. To sum up, she presented a syndrome compatible with a PME.

Results: A complete study was performed to reach the diagnosis, including autoimmune etiology, infectious diseases, paraneoplastic syndromes, and axillary skin biopsy to rule out Lafora Disease, with no relevant findings. A new neuroimaging showed brain atrophy with predominant frontoparietal affection. Finally, a whole exome sequencing was perfomed, discovering a new heterozygous variant of the neuroserpin gen: NM_001122752.1 (SERPINI1):c140T>C p.(Leu47Pro). This variant was absent in her parents’ genome sequency, predicted as deleterious and classified as likely pathogenic.

Conclusion: Mutations in the neuroserpin gene results in a syndrome known as familial encephalopathy with neuroserpin inclusion bodies (FENIB). FENIB usually presents with early cognitive impairment, but there are case reports of PME as clinical presentation (Takao, M. et al. J. Neuropathol 2000;59: 1070-1086), as in our case. The variant we report is not described in the literature or genetics database. Nevertheless, a close change, p.(Ser49Pro) was previously described causing FENIB (Davis, RL. et al. Nature 2001; 401: 376:379). Concerning its localization in the gene and being absent in her parents, this variant is classified as likely pathogenic, becoming the first case described of FENIB presenting as PME with the reported variant.
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Beyond monogenic: widespread genomic influences on the phenotype in Dravet syndrome

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Purpose: Dravet Syndrome (DS), associated with variants in SCN1A, is one of the most common monogenic epilepsies. Whilst DS encompasses a distinct core phenotype, there is marked phenotypic heterogeneity, which is not fully explained by differences between SCN1A variants, or other clinical factors. We explored whether variation across the rest of the genome may contribute to phenotypic diversity within SCN1A-related DS.

Methods: 34 adults with SCN1A-related DS underwent whole genome sequencing. Genomic and phenotypic data were interrogated for the following: 1) Rare variants in additional epilepsy-related genes; 2) polygenic risk scores (PRS) for intelligence and longevity, compared against 919 epilepsy controls, and 1,187 healthy controls; 3) the impact of minor allele homozygosity at rs7587026, which is associated with increased PRS for intelligence and longevity, compared against 919 epilepsy controls, and 1,187 healthy controls; 3) the impact of minor allele homozygosity at rs7587026, which is associated with increased SCN1A expression.

Results: Variants across DEPDC5, CHD2, SCN8A, IQSEC2 were considered to offer independent molecular diagnoses, alongside the SCN1A variant, resulting in composite phenotypes in four individuals, including one individual with DEPDC5 variant and focal cortical dysplasia. PRS for intelligence was significantly lower in DS than epilepsy (p-value=0.0017, Tukey’s test) and healthy controls (p-value=0.004, Tukey’s test). PRS for longevity was significantly higher in DS than epilepsy (p-value=0.011, Tukey’s test), and healthy controls (p-value=0.031, Tukey’s test).

Minor allele homozygosity at rs7587026 was identified in two individuals with null SCN1A variants. Both had mild phenotypes, including seizure freedom in one, which we propose may be explained by increased expression of the normal SCN1A allele.

Conclusion: Whilst a pathogenic variant in SCN1A is the major contributor in DS, it does not act alone. Additional molecular diagnoses, and genome-wide common variation (as highlighted by the significantly lowerPRS for intelligence), contribute to the overall DS phenotype. There is also evidence that genomic resilience (significantly elevated PRS for longevity) amongst adult DS “survivors” may offer protection against premature mortality in DS.

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Insular epilepsy related to KCNT1 missense variants: report of two cases investigated by SEEG

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Purpose: The spectrum of genetic epilepsies is rapidly expanding. Mutations in KCNT1 gene are associated with a broad spectrum of epilepsy and neurodevelopmental disorders such as malignant migrating focal seizures of infancy (MMFSI) and autosomal-dominant nocturnal frontal lobe epilepsy. Here we report clinical and intra-cerebral EEG data of two patients who underwent pre-surgical evaluation for focal insulo-opercular drug-resistant epilepsy related to KCNT1 missense variants.

Case report: Neither of the two patients had intellectual disability, behavioral disorder or psychomotor regression. Seizures were particularly frequent (more than 20 seizures per night) and occurred almost exclusively during sleep. They manifested by a choking sensation and throat noises sometimes followed by hyperkinetic manifestations. The second patient also reported hypersialorrhea, nausea and anarthria. This ictal semiology evoked an insulo-opercular origin, ictal discharge was difficult to see given the artifacts in scalp-EEG. MRI were normal in both patients. Due to a good response to thermocoagulation, the first patient benefited from three SEEG: the first one showed a right focal discharge in the posterior insulo-opercular region while the others revealed bilateral ictal discharges in the anterior and posterior insulo-opercular region. The second patient benefited from one SEEG that revealed bilateral ictal discharge in the anterior and middle part of the insulo-opercular cortex. We did not record discharges within the other cerebral structures explored in the two patients such as the frontal, parietal or temporal lobe. Because of the various seizure patterns that evoked a multifocal epilepsy on the intracranial recordings, we suspected the involvement of KCNT1. A 150-gene panel showed the presence of a pathogenic missense variant in each patient (p.Arg928Cys and p.Arg933His).

Conclusion: KCNT1 missense variants may be associated with epilepsy of focal appearance and should be sought in patients presenting with multifocal insulo-opercular discharges in SEEG.
Two additional cases of developmental and epileptic encephalopathies related to SZT2 pathogenic variants

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Epileptic encephalopathies (EE) and developmental encephalopathies are pathologies with a broad phenotypic spectrum and a high genetic heterogeneity. SZT2 pathogenic variants have been reported in patients presenting with mild and isolated intellectual disability (ID), whereas others presented with severe early onset EE, most often with drug-resistant focal seizures, or less frequently with migrating partial seizures. SZT2 encodes a KICSTOR complex subunit involved in mTOR signaling pathway regulation. The degree of ID varies according to the size of the residual functional protein. Moreover, the reported cases share common morphological features such as macrocephaly, high forehead, ptosis and downsloped palpebral fissures. We report 2 additional cases presenting with developmental encephalopathy related to SZT2 pathogenic variants.

They are two children born from healthy unrelated parents. The older daughter showed severe neonatal hypotonia and was unable to sit without support at the age of 27 months. She also showed oro-facial and hands stereotypes, absent language, macrocephaly, high forehead, and medio-frontal angioma. EEG performed because of episodes of rigidity of the 4 limbs was normal. Brain MRI showed cerebellar atrophy. Chromosomal micro-array (CMA) was normal, as well as metabolic analyses, excluding the hypothesis of CDG syndrome. Thus, trio whole genome sequencing was performed with the hypothesis of mTOR signaling pathway anomaly. Her brother was born with macrocephaly. He presented drug-resistant temporal partial seizures at 5 months of age, with EEG pattern of migrating partial seizures. Brain MRI was normal. CMA and metabolic analyses were normal. Because of this severe early-onset epilepsy, we performed targeted sequencing of a panel of 115 known genes involved in monogenic epilepsies.

We identified 2 new pathogenic compound heterozygous variants in SZT2 in both children. The phenotypes of our patients are consistent with the previous published data and these observations confirm the phenotypic variability of SZT2 pathogenic variants, including intrafamilial variability.

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Genotype and phenotypic features of POU3F3-related disorders

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Purpose: Snijders Blok-Fisher syndrome is a rare neurodevelopmental disorder caused by heterozygous variants in POU3F3. We investigated the genotype and the phenotype of a novel cohort of POU3F3 patients; in addition, we reviewed previously published cases to provide an overview of the current knowledge on the clinic-genetic features of this rare condition.

Method: We collected previously unpublished patients with (likely) pathogenic variants in POU3F3. Data of previously published subjects were retrieved from the literature; the authors of the papers were contacted for further information when necessary.

Results: We identified 30 patients (17 males) with a POU3F3-related disorder; 10 were novel and unrelated. Median age was 7.8 years (range: 1.9-41 years). Twenty-nine/average (96.7%) patients had a mild to profound neurodevelopmental delay mostly affecting speech and cognition and to a lesser degree motor skills. Behavioral or psychiatric comorbidities were present in 24/29 (82.8%); autism spectrum disorder were the most prevalent (12/24; 50%). Early-onset and pharmaco-resistant epilepsy was present in 5/30 (16.7%) patients; both seizures and epileptic encephalopathies were present in 1/30 (3.3%) patients. Early-onset and pharmaco-resistant epilepsy was present in 5/30 (16.7%) patients; both seizures and epileptic encephalopathies were present in 1/30 (3.3%) patients. Early-onset and pharmaco-resistant epilepsy was present in 5/30 (16.7%) patients; both seizures and epileptic encephalopathies were present in 1/30 (3.3%) patients. Early-onset and pharmaco-resistant epilepsy was present in 5/30 (16.7%) patients; both seizures and epileptic encephalopathies were present in 1/30 (3.3%) patients.

Conclusion: We outline the genotypic/phenotypic features of POU3F3-related neurodevelopmental disorders, a rare condition that can encompass early-onset drug-resistant epilepsy with generalized seizures. We suggest that POU3F3 should be considered an additional causative gene of DEEs.
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Linking whole exome sequencing with electronic health care record – a proof of concept epilepsy genomics linkage study

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Purpose: To develop a novel capability pathway to link genetic data with routinely collected data for people with epilepsy. To analyse the influence of rare, deleterious genetic variants on the risk of anti-seizure polytherapy and unscheduled hospital admissions for epilepsy as a proof of concept.

Method: We linked VCFs from whole exome sequencing data with routinely collected primary and secondary care data for people with epilepsy within the Secure Anonymised Information Linkage databank. The study period was January 1, 2000 to January 1, 2019. The study population were adults who had consented to participate in the Swansea Neurology Biobank (SNB) and had DNA sequencing carried out as part of the SNB Epi25 collaboration. We calculated the total number and cumulative burden of rare and predicted deleterious genetic variants (Combined Annotation Dependent Depletion [CADD] score) and the total of rare and deleterious variants in epilepsy and drug metabolism genes. We compared these measures with the following outcomes: (1) anti-seizure medication polytherapy versus monotherapy (2) unscheduled hospital admissions versus no unscheduled hospital admissions.

Results: We linked genetic data for 107 individuals with epilepsy (52% female) to electronic health records. 26% had unscheduled hospital admissions and 70% were prescribed anti-seizure medication polytherapy. There was no significant difference between the outcome groups in terms of the exome-wide and gene-based burden of rare and deleterious genetic variants.

Conclusion: We successfully demonstrated a proof of concept by uploading, annotating, and linking VCF data to anonymised health care records, establishing a pathway that can be followed by other studies, using perhaps different health indicators. We did not detect a genetic influence on real-world epilepsy outcomes, but the study was limited by a small sample size that can be solved with further collaboration and larger exome datasets.

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Eating difficulties and gastrostomy in adults with Dravet syndrome: a single-centre experience

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Purpose: Dravet Syndrome (DS) is characterised by fever-sensitive, drug-resistant epilepsy and intellectual disability. Non-seizure-related comorbidities are common and have a negative impact on quality of life for the person with DS and their caregivers. Difficulties with eating (including anorexia, weight loss and oral motor problems), are frequently reported in surveys of children with DS. In adults with DS, dysphagia is reported as a late feature, at times necessitating gastrostomy. We aimed to determine the extent of eating difficulties, and frequency of gastrostomy, amongst adults with DS in a single UK centre.

Methods: Medical records of adults with DS attending epilepsy clinics at the National Hospital for Neurology and Neurosurgery were reviewed for issues surrounding eating.

Results: 53 adults with DS and pathogenic SCN1A variants were identified; mean age 32.4 years (+/-12.6), 57% female. 31/53 (58%) reported at least one eating difficulty (47% anorexia, 40% weight loss, 13% medication compliance, 9% dysphagia, 8% other). 11/53 (21%) individuals required gastrostomy. The most common issues leading to gastrostomy were anorexia (91%), weight loss (82%) and poor medication compliance (45%). Mean age at gastrostomy was 31.1 years (SD+/-16.0, range:17-59). There was no difference in age, gender, mutation type, or number of antiepileptic medications taken in those with gastrostomy compared to those without. There was a significant association between gastrostomy and use of stiripentol (p=0.025, Fisher's exact test), but no other antiepileptic medication.

Conclusion: Eating difficulties are common in adults with DS. 21% of people with DS at our centre required gastrostomy in adulthood. The factors contributing to eating difficulties and the need for gastrostomy are currently unknown, and are likely multifactorial, including medication side effects and the underlying disease biology. Feeding difficulties should be proactively sought during clinical review of people with DS, and the potential need for gastrostomy should be discussed with caregivers.
Epilepsy and neurodevelopmental disorder associated with TAO1K gene: a relationship to take into account

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Purpose: The new massive sequencing techniques have represented an important advance in the detection of genetic alterations that underlie many neurodevelopmental disorders with unknown cause. In recent years, the list of recognizable syndromes has expanded rapidly. The protein kinase thousand and one amino-acid kinase 1 (TAO1K) has recently been involved in neurodevelopment. Specific mutations in the TAO1K gene are related to alterations in neuronal maturation and cortical neuronal migration, which today we recognize as a potential cause of epilepsy. Likewise, mutations in TAO1K are related to a characteristic clinical spectrum consisting of mental retardation, behavioral alterations, dysmorphic features, hypotonia and joint hypermobility.

Methods: We describe the characteristics of a patient with a developmental encephalopathy with associated epilepsy and a mutation in the TAO1K gene.

Results: This is a 19-year-old woman, born by caesarean section, who was diagnosed with autism spectrum disorder at the age of 28 months. She started with epilepsy 7 years ago on a daily basis and cluster episodes, despite three anti-seizure drugs (PER, LEV and LMT). Brain MRI did not show significant findings. A continuous VideoEEG monitoring was performed. Her seizures presented with brief disconnection from the environment, eye-lid and oral clonic movements, head turning to the right and hypertonia of the right hemibody. Interictal EEG showed epileptiform activity composed of bilateral slow spike-wave complexes predominantly on the left hemisphere. Ictal EEG showed generalized fast activity followed by spike and wave complexes. An exome study reveals the variant NM_020791.2(TAO1K):c.136C>T (p.Arg46*), in heterozygosis in the TAO1K gene. Both parent underwent genetic evaluation being the mother negative (father is pending).

Conclusion: We present a new case of alteration in the TAO1K gene in a patient with a neurodevelopmental disorder and the presence of refractory epilepsy that could be related to alterations in cortical maturation regarding this gene mutation.

Abnormal sensory motor cortex and thalamo-cortical networks in familial adult myoclonic epilepsy type 2

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Purpose: Familial Adult Myoclonic Epilepsy (FAME) is a genetic condition characterized by cortical tremor, myoclonus and epilepsy, underlined by sensory motor cortex hyperexcitability. Besides pericentral cortical structures, the impairment of subcortical networks might play a pathogenetic role, via the thalamo-cortical pathway. The mechanisms underlying cortical-subcortical circuits dysfunction, as well as their impact on clinical manifestations, are unknown. The main aims of our study were to study the cortical sensory motor as well as thalamo-cortical networks in genetically confirmed FAME2 patients and to establish reliable neurophysiological biomarkers for the diagnosis.

Methods: In 26 FAME2 subjects, harbouring the intronic ATTTC repeat expansion in the STARD7 gene, 17 Juvenile Myoclonic Epilepsy (JME) patients and 22 healthy controls (HC), we evaluated the facilitatory and inhibitory circuits within the primary motor cortex (M1) using single and paired-pulse transcranial magnetic stimulation (TMS) paradigms. We also probed the excitability of the somatosensory (S1) cortex as well as the thalamo-S1 connection by using ad hoc somatosensory evoked potential (SEP) protocols.

Results: FAME2 patients displayed increased facilitation and decreased inhibition within the sensory motor cortex compared with JME patients (all p < 0.05) and HC (all p > 0.05). SEP protocols displayed a significant reduction of early high-frequency oscillations and less inhibition at paired-pulse protocol, suggesting a concomitant failure of thalamo-S1 circuits. Disease onset and duration, and myoclonus severity did not correlate neither with sensory motor hyperexcitability nor thalamo-cortical measures (all p > 0.05). Patients with a longer disease duration had a more severe myoclonus (r = 0.467, p = 0.02) associated to a lower frequency (r = -0.607, p = 0.001) and higher power of tremor (r = 0.479, p = 0.02).

Conclusions: sensory motor cortical and thalamo-cortical circuits are involved in the pathophysiology of FAME2 even if these alterations are not associated with clinical severity. TMS-based measurements display an higher accuracy than SEP parameters to reliably distinguish FAME2 from JME and HC.
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10 years of CGH for epilepsy indication at the University Hospital of Lyon (France) - diagnostic yield, identified CNVs and strategy in the genome sequencing era

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Purpose: The advent of CGH in the early 2010s was a revolution in the diagnosis of epilepsy. Increasingly accessible genome sequencing is certainly the next step. The possibility of detecting CNVs by this approach led us to quantify the diagnostic contribution of CGH for epilepsy since its start in this indication at the University Hospital of Lyon in 2011 to consider the future diagnostic strategy.

Method: We included all postnatal CGH data (180k chip), performed between 2011 and 2021 for epilepsy (syndromic or not). We analysed the CNVs identified to calculate the diagnostic yield (before and after reinterpretation), characterise the CNVs (copy number, size, genes) and the risk of incidental data. The evaluation of gene content is based on the 139 genes of the routinely used national epilepsy panel

Results: Of the 9180 postnatal CGH performed during the study period, 927 were performed for epilepsy. 12.6% patients (112) were carriers of ≥ 1 of 131 CNVs interpreted as (probably) pathogenic (94 losses 37 gains). 67% of these (probably) pathogenic CNVs > 1Mb, 16% are 400k-1Mb and 16.8% are < 400 kb. 54 (41%) CNVs at least partially cover the panel. This corresponds to 46 patients (41%) for whom the panel would have provided at least a partial diagnosis. Of the 139 panel genes, 46 (33%) are represented ≥ 1 in the CNVs found. 8% of diagnosis are „incidental“. Excluding incidental, yield after reinterpretation is 8.6% (77 patients): consistent with the literature (5-13%)

Conclusion: Our study highlights the CNV involvement in this heterogeneous indication. We will present the identified CNVs (including gene content). Thus, until the genome is as accessible (cost and time), CGH remains relevant for syndromic epilepsy. By adding genomic region captures at recurrent CNVs to the panel, the updated version will be even more efficient for isolated epilepsies.

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A rare cause of recurrent FIRES

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Purpose: We aim to report the clinical picture and the diagnostic findings in a patient with a rare cause of recurrent status epilepticus following febrile illnesses. The patient presented, following systemic viral infections, three episodes characterized by confusion, behavioural alterations and seizures requiring intensive care admission. Between these episodes the patient recovered completely without developing epilepsy.

Method: The patient underwent an extensive diagnostic work-up, including microbiological and autoimmune tests on blood and cerebrospinal fluid, neuroimaging, EEG-monitoring, muscle biopsy and neurometabolic tests, an epilepsy gene panel and whole exome sequencing (WES). Family segregation studies were also performed.

Results: On all three occasions, the patient presented, following a febrile viral infection, a clinical picture characterized by psychomotor agitation alternating with excessive sleepiness, without focal neurological signs; soon after, the patient developed a focal motor status epilepticus, that required admission to the intensive care unit. The patient was first treated with Acyclovir followed by steroid treatment and intravenous immunoglobulins with full recovery following each episode. All the diagnostic tests were negative except for WES that unravelled a homozygous pathogenic variant of the FADD gene, encoding for a protein involved in the apoptosis of immune cells and in the innate immune response.

Conclusion: FIRES (Febrile Infection-related Epilepsy Syndrome) is a rare condition, in most cases cryptogenic. Pathogenic variants in FADD gene have so far been described in seven other patients with a clinical picture similar to that of our patient but generally more severe. We therefore report a rare genetic aetiology of recurrent FIRES-like episodes.
A novel SCN1A missense mutation in familial Dravet syndrome

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Purpose: To describe a familial Dravet syndrome associated with a missense SCN1A mutation in exon 20, previously described as a de novo mutation.

Method: Clinical characterisation and results of genetic testing are presented.

Results: Three sisters were diagnosed of Dravet syndrome between 38-44 years old. Their father and at least three paternal cousins and a daughter of one of them suffered from epilepsy. All relatives from the father’s side (including the father) had behavioural problems.

The father had epileptic seizures during lifespan, although well controlled with valproate. He was diagnosed of Alzheimer’s disease when he was 64 years old and died 6 years later. Neuropathological hallmarks of the disease were confirmed in brain tissue.

All three sisters had from mild to moderate intellectual disability. Epileptic onset was at 6 months of age, triggered by fever. Two of them underwent callosotomy at 12 and 18 years old, improving seizure control. However, the sister with the greatest disability was not intervened, suffered drug resistant epilepsy and died of hypercapnic respiratory insufficiency at the age of 42. The remaining sisters have mild ataxia, parkinsonism and limb dystonia. They are seizure free for the last four years, with great benefit of topiramate. EEG in November 2021 showed intermittent bitemporal theta slowing, without epileptiform activity.

Genetic testing was performed in the three sisters in 2012, showing a missense mutation in SCN1A p.Gly1332Glu (c.3995G>A) in exon 20. This mutation has been previously associated with de novo SMEI (severe myoclonic epilepsy of infancy).

Conclusions: To our knowledge, this is the first time that a mutation in SCN1A p.Gly1332Glu (c.3995G>A) in exon 20 is associated with familial Dravet syndrome. Although confirmed genetic diagnosis has only been possible in three sisters, we hypothesize that other relatives may have the same mutation with mild phenotypic expression.

Epileptic spasms due to CAMK2 gene mutations: description of two cases

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Purpose: CAMK2 is a Ca2+/calmodulin-dependent serine/threonine protein kinase involved in the regulation of synaptic plasticity and ionotropic glutamate receptors activity. This enzyme is composed by distinct subunits, encoded by separate genes (1). Mutations in subunits alpha (CAMK2A) and beta (CAMK2B) are associated to autosomal dominant mental retardation (OMIM #617798 and #617799). Aim of this study is to report the electro-clinical features of two patients with epilepsy, carrying pathogenic mutations in CAMK2 genes.

Methods: We retrospectively reviewed the medical charts of two patients carrying a heterozygous de novo pathogenic mutation in CAMK2A (c. 857C>A; p.Thr286Asn) and CAMK2B (c.416C>T,p.Pro139Leu). We collected clinical, genetic, EEG, neuropsychological, and radiological findings of both patients.

Result: Patient with CAMK2A mutation is a 6 years old girl, with a severe developmental delay. Epilepsy onset was at 5 months, with tonic seizures and epileptic spasms, resistant to anti-seizure medications. EEG showed poor background activity with multifocal epileptiform abnormalities. She still has generalized hypertonic seizures, multiple per day, hypotonic tetraparesis and dyskinesia. Brain MRI showed microcephaly and cerebellar atrophy.

Patient with CAMK2B mutation is a 4 years old boy, with severe developmental delay. Epilepsy onset was at 7 months, with focal seizures followed by epileptic spasms, which were treated with vigabatrin, with remission of spasms but persistence of focal seizures. EEG showed poor background activity with multifocal epileptiform abnormalities, mainly over posterior regions. He did not reach the autonomous walking nor language. He has poor visual attention, motor stereotypes and impulsive biting behavior. Brain MRI was normal.

Conclusion: In Literature, only 29 patients carrying CAMK2 mutations have been reported so far (2,3). Epilepsy is not described in all patients and only one patient had epileptic spasms. Description of these two patients suggests that epilepsy, and particularly epileptic spasms, might be a more frequent feature than expected in this disease.
Cortical visual impairment in CDKL5 deficiency disorder

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Purpose: CDKL5 deficiency disorder (CDD) is a developmental encephalopathy caused by pathogenic variants in the gene cyclin-dependent kinase-like 5. Cerebral visual impairment (CVI) is frequent in patients with CDD and it is recognized as a specific feature of the pathology, and it is probably in correlation with neurodevelopmental outcome and epilepsy severity. The aim of our study was to evaluate clinical and electrophysiological profile of CVI in patients with CDD, to correlate various aspects of visual function to neurodevelopmental and epileptic features.

Methods: The study included all patients with CDD from the Italian National Pathology Registry. All patients underwent neurological examination, a disease-specific functional assessment, structured clinical evaluation of visual functions, including pattern reversal visual evoked potential (VEP), and a detailed monitoring of epileptic features, including video-EEG.

Results: All the 11 patients recorded in the CDKL5 national registry, 10 females and one male, age range of 1.5 to 24 years (mean 9, SD 7.7, median 6.5), were enrolled. Visual function is impaired in all patients; in particular, visual fields, visual acuity, contrast sensitivity, and stereopsis were consistently abnormal whereas other aspects, such as fixing and tracking, were relatively preserved. Pattern reversal VEP was abnormal in nearly 80% of our patients. No correlation was found among CVI severity, age, level of psychomotor development, EEG abnormalities, and pathology stages even if an overall less abnormal EEG pattern was more often associated with better visual results.

Conclusion: In conclusion, CVI can be considered as a major feature of CDD with a diffuse involvement in several behavioral and electrophysiological aspects. Larger cohorts will help to better clarify the possible prognostic role of EEG severity in predicting both visual and developmental abnormalities.

The clinical utility of genetic testing on patients with developmental and epileptic encephalopathies

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Purpose: The purpose of this study is to investigate the clinical utility of genetic testing in patients with developmental and epileptic encephalopathies (DEE).

Method: All patients with epilepsy diagnosis treated at Kuopio Epilepsy Center are offered the possibility to participate to a study "Biomarkers of Epilepsy". Among participants we identified 303 patients with developmental and epileptic encephalopathies (DEE). 36 of these patients had an identified etiology after routine clinical examination (including acquired structural causes, previous central nervous system infections and autoimmune epilepsies) and 267 had an unknown etiology before genetic evaluation.

If the etiology was unknown Whole Exome Sequencing (WES) including investigation on deletions and duplications was performed.

Results: We have at the moment analysed results of 182/267 DEE patients with unknown etiology. Likely causative genetic mutations or chromosomal changes were recognized on 62% (112/182) of patients. Pathogenic mutations on single genes were discovered in 42% (76/182) and chromosomal changes (including copy number variants) in 14% (25/182) of patients. Most common causes were tuberous sclerosis (8%) and SCN1A mutations (6%). 6% (11/182) of patients had more than one mutation probably affecting their phenotype. In addition, variants of unknown significance on previously recognized epilepsy genes were discovered in 15% (34/182). We also discovered possible causative mutations on candidate genes not yet linked with epilepsy in 4% (8/182) of patients.

Conclusion: We could verify genetic etiology on 62% of the DEE patients. Most of these etiologies are pathogenic mutations on single genes rationalizing the use of WES early in the diagnostic process. Recognizing genetic causes has relevance for choosing the right therapy in many patients and the era of precision medicine seems to become closer as the targeted treatments are arising.
Movement disorders as a part of the SCN8A-phenotypic spectrum

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Purpose: The SCN8A phenotype encompasses a variety of neurodevelopmental disorders including epilepsy, intellectual and motor disability, and autism. Movement disorders are not rarely associated with this broader phenotypic spectrum. We aim to describe the prevalence and characteristics of SCN8A-related movement disorders, underling their impact on patients’ life.

Method: We performed a literature review, selecting subjects with SCN8A-diseases and extrapyramidal symptoms. We also collected detailed data from families and their referring physicians through a structured questionnaire and by rating scales for dyskinesia (INAS), ataxia (SARA), dystonia (UDRS), and myoclonus (UMRS).

Results: In total, 124/645 (19%) patients (133 papers) in ages ranging from 0-45 years, were reported with movement disorders. Ataxia was the predominant sign (68/124, 54.8%), followed by dystonia (32/124, 25.8%), dyskinesia (31/124, 25%), and myoclonus (17/124, 13.7%). A combination of the four disorders was seen in 22/124 (18%) subjects.

Neurological examination showed hypotonia in 53/124 (43%), spasticity in 21/124 (17%), and tremor in 14/124 (11%). ID was reported in 51.6%, epilepsy in 90% and ASD in 12% of the subjects.

Rating scales and questionnaires were returned from 25 patients. Motor disability was a common finding (77%) leading to poor self-sufficiency. Ataxia had the highest score on the rating scale (SARA>30/40) and was associated with severe developmental delay. Dystonia and dyskinesia were less invalidating and were related to moderate-to-severe ID. Myoclonus might be subtle and likely underestimated; often it was associated with cortical blindness.

Interpretation: Ataxia, dystonia, dyskinesia, and myoclonus are frequently diagnosed in SCN8A-epilepsy patients. An overlap between epilepsy, cognitive-motor disability, and movement disorders is common often resulting in a slightly worst quality of life.
The efficacy of Levetiracetam in SCN8A-epilepsy

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Purpose: In pursuit of precision medicine, there is a need for recommendations for effective therapy. For SCN8A-epilepsy, the most common effective drugs are sodium channel blockers (SCBs), while Levetiracetam (LEV) has a controversial effect. We aim to further investigate the efficacy of LEV in SCN8A-epilepsy.

Method: We made a systematic literature review of SCN8A-epilepsies treated with LEV and reviewed all the data included in our database. From a total cohort of 645 subjects, we selected the ones having taken LEV. We elaborated two specific questionnaires, one for clinicians and one for families, collecting further demographic and genetic data, as well as the electro-clinical data at baseline and during LEV treatment.

Results: We enrolled 193 subjects, with a median age of 5.7 years (range: 0.5 months-66 years). Details about LEV response were available for 151 subjects. LEV did not have an effect in 101/151 (67%), and seizure worsening was reported in 28/151 (18%). A few patients achieved either <50%-of-seizure-reduction (5/151, 3%), >50%-of-seizure-reduction (7/151, 5%), or seizure freedom (10/151, 7%), mostly among subjects with a mild phenotype, with generalized epilepsy and with SCN8A-LoF (loss-of-function) variants.

62 questionnaires have been returned, confirming a high prevalence of subjects with no response to LEV (37/62, 60%) or seizure worsening (13/62, 20%). Mental retardation was associated with poor response and associated with more side effects and earlier discontinuation of LEV therapy. Regarding LEV tolerability, 20/62 (32%) subjects reported adverse effects, 13/62 (21%) had to stop the treatment also because of the side effects.

Conclusion: We highlight that, in most cases, LEV had no effect or worsened seizures in subjects with SCN8A-epilepsy, compared with other anti-seizure medications, both SCBs and non-SCNBs. Further studies may lead to a better understanding of the mechanisms of the effect of LEV in sodium channelopathies.
The p.Glu787Lys variant in the GRIA3 gene causes developmental and epileptic encephalopathy mimicking structural epilepsy in a female patient

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Purpose: The purpose of this article was to describe a new case of X-linked DEE in a female patient associated with a de novo missense mutation (c.2359G>A; p. Glu787Lys) in the GRIA3 gene, characterized by a phenotype different to those so far described and partly suggestive of focal epilepsy of a structural cause. We investigated the functional effects of p.Glu787Lys in iGluR3 protein in fibroblasts. Additionally, we intended to discuss our patient’s electro-clinical presentation and investigate a possible pathophysiological mechanism leading to the disorder.

Method: First, we determined whether the patient’s genetic variant (c.2359G>A; GRIA3) was affecting the Flop or Flip alternative segments splicing in exon 14. Second, as iGluR3 is a glutamatergic receptor, we investigated fibroblasts’ response to glutamate treatment.

Results: We found significantly lower iGluR3 expression in the patient’s fibroblasts than in controls and different responses to glutamate treatment.

Conclusion: These results showed that p.Glu787Lys decreases the levels of GRIA3Flop mRNA, consequently affecting the expression levels of a subunit 3 of the glutamate AMPA receptor.

Whole-exome sequencing of ovarian teratoma in NMDAR-antibody encephalitis

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Objective: N-methyl-D-aspartate receptor (NMDAR)-antibody encephalitis is the most common form of autoimmune encephalitis, about 40% of which is caused by ovarian teratoma. However, it is unknown why only a small population of ovarian teratoma causes the autoimmunity while the majority of the teratoma don’t. This study aimed to investigate any driver mutations specific to the NMDAR-associated teratoma to reveal the autoimmunity mechanism.

Method: We included 17 ovarian teratomas derived from 15 patients with NMDAR-antibody encephalitis and 18 control ovarian teratoma from 30 patients without encephalitis. All the samples were genotyped by the SureSelect V6 Post Exome Capture kit (Agilent, CA, USA). The exome data were analyzed with R version 4.06 (Vienna, Austria) and the MUTALISK program (National cancer center, Goyang-si, Korea).

Result: The two groups with and without NMDAR-antibody encephalitis had a mean age of 23.9 and 24.4 years, respectively. The average teratoma size was smaller in the group with encephalitis (3.0±2.1 cm vs 10.9±2.1, respectively). With the criteria lower than 1% of allele frequency with 1000 genome phase 3 (1000Gp3) and the Exome Aggregation Consortium (ExAC), 34 exomes were passed in our samples. Of these, no exome showed significantly different mutations between the groups of teratoma with and without NMDAR-antibody encephalitis. From the MUTALISK analysis, there was no significant difference in the mutation pattern signature in exomes between the two groups.

Discussion: This study shows that there is no difference in the mutation profile in protein-coding genes between the ovarian teratoma causing NMDAR-antibody encephalitis and the control teratoma. This result implies that post-transcriptional immune pathogeneses are involved in the autoimmune recognition of ovarian teratoma with NMDAR-antibody encephalitis.
Effects of the ketogenic diet and modified Atkins diet in patients with STXBP1-related encephalopathy

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**Purpose:** To review efficacy of ketogenic diet in patients with STXBP1 mutations.

**Methods:** We investigated the effects of a ketogenic diet (KD) and modified Atkins diet (MAD) in patients with STXBP1-related epilepsies. This study included 12 patients who had STXBP1 encephalopathy and drug-resistant epilepsy. All patients were treated with KD or MAD between January 1, 2005, and June 30, 2021 at Severance Children’s Hospital.

**Results:** The median age at the initiation of the diet was 4.5 months (interquartile range, IQR: 3.0–9.3). The median age at seizure onset was 1.5 months (IQR, 0–3). Median duration of the KD or MAD was 6.5 months (IQR: 2.8–13.3). Nine (75%) patients had Ohtahara syndrome, two (16.7%) had West syndrome, and one (8.3%) had Lennox-Gastaut syndrome. Three (25%) patients achieved complete seizure freedom with the KD or MAD, and remained seizure-free for 2, 3, and 7 years each. Electroencephalographic findings improved in all three patients. All three remained seizure-free even after the dietary therapy was discontinued. One patient (8.3%) in the seizure-free group could discontinue the antiseizure drugs.

**Conclusions:** KD and MAD can be an effective treatment option for patients with drug-resistant epilepsy related to STXBP1 gene mutations.

First seizure. Using EEG to distinguish epilepsy vs non-epilepsy patients after a first event

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**Purpose:** Electroencephalography (EEG) plays a central role in diagnosis and management of epilepsy. In this work we want to investigate how epilepsy is presented in EEG early on by evaluating how advanced EEG features differ between epilepsy and non-epilepsy patients after a first event.

**Method:** The group analysis is performed on a retrospective EEG dataset of 640 patients from Geneva University Hospital. All EEGs were taken after first admission of the patients to the hospital following a first event. Patients were grouped based on follow-up in having epilepsy (n=367) or not (n=264). The non-epilepsy group included vagal syncope, provoked seizures, brain tumors etc. After pre-processing, several EEG metrics were computed including spectral band powers, functional connectivity based on phase locking value (PLV) and amplitude envelope correlation (AEC), and graph measures (node degree and global efficiency). To reduce local variability, the metric values of the individual electrodes are averaged over groups in the front left (FL), front right (FR), back left (BL) and back right (BR) regions. The differences at group level were assessed using an ANOVA F-test, corrected for multiple comparisons by controlling the False Discovery Rate at α=0.01.

**Results:** We found a statistically significant increase in delta power (p<1e-05) and decrease in beta power (p<1e-04) in epilepsy patients compared to non-epilepsy patients. A significant increase in AEC and the related global efficiency was identified in patient with epilepsy compared to those without (p<1e-04). For all measures, the differences were consistent across all regions. For the PLV we did not find any significant difference between groups.

**Conclusion:** In this work we show that there exist group differences for EEG-based metrics between epilepsy and non-epilepsy patients. With these results we hope to gain a better understanding of the general mechanisms of epilepsy and how it's presented in resting state EEG.
Radiomics-based magnetic resonance imaging analysis potentially differentiate patients with juvenile myoclonic epilepsy from healthy controls

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Purpose: Recently, advanced imaging analysis methods revealed microstructural and functional brain abnormalities in patients with juvenile myoclonic epilepsy (JME) (Cao B et al. Epilepsy Res. 2013; 106:370-7). Radiomics is capable of obtaining information such as intensity distributions, spatial relationships, textural heterogeneity, and shape descriptors (Aerts HJ et al. Nat Commun. 2014; 5:4006). This study aimed to build and validate radiomics prediction models that could discern patients with JME from healthy controls (HCs).

Method: A total of 129 subjects (97 JME patients and 32 HCs) were assigned to a training (n=90) or a test-validation set (n=39) group. Diagnosis of JME was performed based on clinical and EEG features. Radiomics features were extracted from 20 regions of interest from T1-weighted MRI images. Several machine learning models were trained with the patients' radiomics features during training sets, and they were validated with test-validation sets.

Result: The seven tested radiomics models – light gradient boosting machine, support vector classifier, random forest, logistic regression, extreme gradient boosting, gradient boosting machine, decision tree – showed an area under the curve (AUC) of 0.82, 0.81, 0.78, 0.78, 0.77, 0.76, 0.67, respectively. The best-performing model, the light gradient boosting machine, demonstrated an accuracy, precision, recall, and F1 score of 0.79, 0.82, 0.93, and 0.87, respectively. Radiomics features including the putamen and cerebral peduncle ranked as the most important for suggesting JME.

Conclusion: Radiomics models with multiple regions of interest in routine brain MRI could be an auxiliary tool in discerning patients with JME from HCs.

Automated characterisation and lateralisation of hippocampal sclerosis from MRI in children with epilepsy

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Purpose: Recent studies have demonstrated lateralisation of hippocampal sclerosis (HS) in adults using surface-based automated methods on presurgical MRI (Caldairou et al., 2021). To date, no such tools have been developed for children. In this study, we characterised the morphological abnormalities of the hippocampus in children with HS, and utilised these features to carry out automated lateralisation of the abnormality.

Method: This study was performed on 23 children from Great Ormond Street Hospital with histologically confirmed HS and 20 healthy children. The open-source HippUnfold software (DeKraker et al., 2021), was used to segment and unfold hippocampi into surface-meshes from T1w MRI images. Multiple surface-based features — cortical thickness, gyrifications, intrinsic curvature, T1w and FLAIR intensity — were also extracted. Features were smoothed, normalized by controls and asymmetry were computed to quantify differences between left and right hippocampi. Areas under the curve (AUC) and paired student t-tests on feature distributions were used to compare the ipsilateral hippocampus to the contralateral healthy hippocampus in children with HS. Hippocampal features were used to train a Multilayer Perceptron (MLP) classifier (hidden layer size = (5,10), activation = ‘relu’) to lateralise HS. MLP performances were evaluated using stratified 10-fold cross-validation.

Results: Ipsilateral hippocampi were characterised by significantly smaller thickness, smaller gyrification, higher intrinsic curvature and FLAIR hypointensity compared to contralateral hippocampi (AUCs > 0.98; p-values < 0.0001), but no difference in T1 intensity. Using these features the MLP classifier was able to lateralise HS with 95% overall accuracy.

Conclusion: Analysis of hippocampi in children with HS identified that the presurgical MRI features — density of gyrification, thickness, intrinsic curvature, and FLAIR intensity — significantly differed between abnormal hippocampi and contralateral hippocampi. These features enabled highly accurate lateralisation of the abnormality and could be used to automate the lateralisation in surgical candidates with suspected HS.
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The effect of interictal spikes on the brain regions involved in sudden unexpected death in epilepsy: a pilot study

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Purpose: The aim of the present study is to investigate the effect of interictal epileptiform discharges (IEDs) on the functional connectivity (FC) between cortical and subcortical brain regions known to be involved in the SUDEP (Sudden Unexpected Death in Epilepsy) and the rest of the brain.

Methods: From the entire dataset of epilepsy patients investigated with EEG-coregistered to fMRI (EEG-fMRI), one patient affected by focal drug-resistant epilepsy was classified as “Probable SUDEP” (Nashef et al. 2012). This case was matched with 2 high-risk and 2 low-risk patients for SUDEP according to age at the scan, sex, and epilepsy syndrome (La et al. 2019). Seven Region of Interest (ROIs) were selected based on previous published data (Anterior Cingulate Cortex, Insula, Brainstem, Thalamus, Amygdala, Putamen). The IED-related functional connectivity between the selected ROIs and the rest of the brain was investigated through a Psychophysiological Interaction (PPI) analysis and, in order to compare the resulting PPI-related maps, a Fixed Effect approach was applied.

Results: Both SUDEP case and high-risk patients showed increased spike-related FC between the Brainstem, Thalamus, left Amygdala, Insula, Putamen, ACC, and the inferior parietal lobule, inferior frontal gyrus, and middle frontal gyrus, all lateralized to the right side. On the contrary, common patterns of reduced IED-related FC between the Brainstem, Insula, Putamen, ACC, and the bilateral superior and medial frontal gyrus emerged.

Conclusions: The results demonstrated that in the SUDEP case and high-risk patients, IEDs modulate the connectivity of brain networks implicated in the maintenance of consciousness and in the regulation of the cardiovascular system, both elements well known to be involved in the pathogenesis of SUDEP. Our data support the hypothesis that a facilitating environment for SUDEP to happen can result from interictal activity not only from seizure’s occurrence.

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The role of the amygdala in ictal central apnea: new insights from brain MRI structural morphometry and long-term video EEG monitoring

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Purpose: Ictal central apnea (ICA) has been recently considered a potential localizing sign in temporal lobe epilepsy and a hint of amygdala involvement in the epileptogenic network. Advanced neuroimaging techniques may be used to find valuable biomarkers for ictal apnea occurrence.

Method: To describe the electroclinical characteristics of temporal lobe seizures with ICA, data from video EEG Long-Term Monitoring with extensive polygraphic recordings were collected among a population of 49 patients with seizures recorded from April 2020 to October 2021. To evaluate possible structural morphometric differences in relation to the occurrence of ICA, 3T brain MRI scans were post-processed with FreeSurfer to extract cortical thickness and subcortical volumes in three groups of subjects (7 patients with temporal lobe seizures with ICA and 10 patients with temporal lobe seizures without ICA, and 30 healthy controls).

Results: 7 patients (4 males; aged 20-55 years) had apnea-related seizures. Among these patients, 21 seizures were recorded, and ictal apnea was observed in 80.9 % of seizures. Oxygen desaturation occurred in 5/7 with a nadir ranging from 92 to 74 %. The morphometric analyses revealed a significant increase in volume of the amygdala ipsilateral to the epileptic focus, and more specifically of the basolateral complex, in the patients with ICA compared to healthy controls (p=.000) and patients without ICA (p=.023).

Conclusion: Our findings, while confirming the key role of the amygdala in temporal lobe epilepsy, offer new insights on subtle structural modifications of the amygdala and its subnuclei as possible morphological biomarkers of ICA.
Clinical benefit of the HARNESS-MRI protocol for focal epilepsy: a monocenter prospective study

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Purpose: To evaluate in a real clinical scenario the sensibility and specificity of the ILAE-recommended “Harmonized neuroimaging of epilepsy structural sequences”- HARNESS protocol (Bernasconi et al., 2019) in patients with focal epilepsies.

Method: We prospectively enrolled patients who underwent a structural brain HARNESS-MRI protocol for diagnostic purposes between March 2020 and June 2021. Inclusion criteria were:

a) electro-clinical diagnosis of focal epilepsy;

b) a previous MRI scan performed not respecting the HARNESS protocol (pre-HARNESS);

c) MRI visual inspection obtained by the same trained experts. Radiological reports were reviewed and compared between HARNESS and pre-HARNESS considering the following items:

(i) number of positive and negative MRI;

(ii) distribution of the MRI-positive scans according to type of epileptogenic lesions classified in

1. Focal Cortical Dysplasia (FCD);

2. Hippocampal Sclerosis;

3. Other malformations of cortical development

(i.e. polymicrogyria);

4. Dual pathology. Brain tumors were excluded.

Statistical analysis was performed using a non-parametric within-subject analysis. Diagnostic accuracy, sensibility, and specificity of the HARNESS-MRI protocol were estimated.

Results: 70 adult focal epilepsy patients were enrolled. The pre-HARNESS protocol revealed 42 (60%) MRI-negative and 28 (40%) MRI positive. The HARNESS protocol showed 30 MRI negative (43%) and 40 MRI positive (57%). In 12 out of 42 pre-HARNESS MRI-negative patients, the negativity was not confirmed, and a potentially epileptogenic lesion was detected (p = .003). The most common unrecognized diagnosis was FCD (p = .008). Estimated accuracy of the HARNESS-MRI protocol was 81%, the sensibility 96%, and the specificity 71%.

Conclusions: This is the first study to evaluate prospectively the real-world impact of the HARNESS protocol on the diagnosis of focal epilepsy. We show that the adoption of a standardized and optimized MRI protocol allows to identify a higher number of potentially epileptogenic lesions thus impacting concretely on the clinical management of focal epilepsy patients.

Intracranial volume and lithium-related cognitive dysfunction in temporal lobe epilepsy

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Purpose: Progressive gray matter (GM) volume reductions beyond the epileptogenic area have been described in temporal lobe epilepsy (TLE). There is less evidence regarding correlations between GM and white matter (WM) volume differences and multi-domain cognitive performance in this setting. We aimed to investigate extratemporal GM and WM changes and their correlation with visuospatial performance in TLE patients.

Method: Cross-sectional study comparing global and regional brain volume data from 34 TLE patients and 30 healthy controls. 3D T1-weighted sequences were obtained on a 3.0 T magnet and the brain parcellation was performed with Freesurfer. Data were analyzed using age and sex-adjusted linear regression models. Global and regional brain volumes and cortical thickness in patients were correlated with standardized visual memory, visuoperceptual, visuospatial, and visuoconstructive parameters obtained in a per-protocol neuropsychological assessment.

Results: TLE patients had smaller volume fractions of the deep GM structures, putamen and accumbens. Patients had worse scores in visual memory, attention, processing speed, and executive functions. Correlations were found between:

1) visual memory and precuneus and inferior parietal cortical thickness;

2) visuoperceptual performance and precuneus and supramarginal WM volumes;

3) visuospatial skills and precuneus, postcentral, and inferior and superior parietal WM volumes;

4) visuoconstructive performance and inferior parietal WM volume.

Conclusion: Brain volume loss is widespread in TLE. Volumetric reductions in parietal lobe structures were associated with visuoperceptual cognitive performance.
Purpose: The advent of high resolution brain imaging and advanced computational tools has evidenced that the occurrence of seizures is dependent on local organization of brain networks. However, little is known about how network reorganization increases the vulnerability for paroxysmal events. Here, we evaluate the network vulnerability to induced ‘virtual lesions’ in patients with focal epilepsy by using a generative model.

Methods: Structural 3T T1 MRI data of 40 patients (30±6 years; 17 male) with focal epilepsy (FE; 31 with temporal, 9 with extratemporal) and 35 healthy subjects (HS; 23±5 years; 14 male) were processed by using FreeSurfer. Extracted cortical thickness at 68 regions served for the reconstruction of morphometric networks. The graph theoretical framework was applied to analyze the vulnerability of networks to random and targeted attacks. Network topology organization was quantified by means of clustering, local efficiency, and path length.

Results: In contrast to HS, morphometric networks of FE patients were characterized by comparable vulnerability (all p>0.05, corrected) to random attacks (i.e. random removal of brain regions) but by a higher vulnerability (all p<0.05, corrected) to targeted attacks (i.e. removal of brain regions according to their importance for network organization). Regions important for network organization (i.e. hubs) were less in number and located in different brain regions in FE patients (left superior temporal and right paracentral gyr) compared to HS (left anterior cingulate, right superior temporal, and right supramarginal gyr). The local topological organization of morphometric networks in FE patients was marked by increased segregability – higher clustering coefficient (t=2.23, p=0.02) and local efficiency (t=2.41, p=0.01), whereas at the global level by decreased integrability – higher path length (t=1.90, p=0.04), when compared to HS.

Conclusion: Increased vulnerability of morphometric networks in FE patients may stem from the reorganized network topology and serve as a mechanism facilitating seizure occurrence.

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[11C]metoclopramide PET-MR for the in vivo exploration of P-glycoprotein function at the blood-brain barrier in patients with drug-resistant and drug-sensitive epilepsy

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Purpose: Overactivity of the ABC transporter P-glycoprotein (P-gp) in the seizure origin of patients with drug-resistant temporal lobe epilepsy has been demonstrated in positron emission tomography (PET) studies using the radiotracer (R)-[11C]verapamil (Feldmann M et al. The Lancet Neurology 2013; 12(8): 777-85.). (R)-[11C]verapamil has several shortcomings, such as a complex study setup, which requires two subsequent PET scans before and after pharmacological inhibition of P-gp to show P-gp overactivity. The novel radiotracer [11C]metoclopramide is a weak P-gp substrate. Previous studies in healthy volunteers have revealed the suitability of [11C]metoclopramide PET to investigate P-gp related changes at the blood-brain barrier, including overactivity. This innovative study setup in epilepsy patients could help distinguish drug-resistant from drug-sensitive foci in lesional and non-lesional epilepsies.

Method: Researchers in the Paris-Saclay University and the Medical University of Vienna plan to perform a single [11C]metoclopramide PET-MR in 80 focal epilepsy patients and in 20 healthy volunteers, in order to assess and compare the P-gp function in epilepsy onset zone with healthy brain tissue. The study was approved by the local Ethics Committees.

Results: Ten healthy volunteers and five patients with focal epilepsy (one seizure free focal epilepsy, one drug resistant focal epilepsy with multiregional seizure onset zones, one drug resistant nonlesional focal epilepsy, and two with drug resistant epilepsy with epileptogenic structural lesion) underwent so far a single [11C]metoclopramide PET-MR. None of the participants experienced any side effects. An analysis of preliminary data is underway.

Conclusion: We performed for the first time[11C]metoclopramide PET-MR in epilepsy patients and our preliminary results confirm the feasibility and the safety of [11C]metoclopramide PET-MR in patients with epilepsy. Clinically relevant results will hopefully arise from the inclusion of a larger cohort of patients.

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Integration of high-resolution ultra-high-field 7T magnetic resonance imaging into clinical care of epilepsy patients: first results

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Purpose: Recently, ultra-high-field MR imaging at 7 Tesla has received CE mark and FDA clearance. Several pre-clinical studies demonstrated improved diagnostic yield over 3T-MRI in depiction and characterization of epileptogenic lesions. The goals of this study were to establish a clinically applicable epilepsy imaging protocol at 7T-MRI and to evaluate the new imaging protocol in clinical workflow.

Method: We analysed radiological reports of patients with known epilepsy who received 7T-MRI with the new epilepsy protocol and who previously received 3T-MRI according to the ILAE recommendations. 7T-MRI was performed using MAGNETOM Terra (Siemens Healthcare, Germany) and the CE-marked single channel transmit and 32-channel receive head coil (Nova Medical, USA). The 7T-imaging protocol comprised T1 MP2RAGE (3D isotropic, 0.6mm), T2 TSE (transversal, 1.5mm), T2 TSE (transversal, 0.7mm), T2 TSE (perpendicular to the long and short axis of the hippocampus, 0.7mm), FLAIR SPACE (3D isotropic, 0.7mm), SWI (transversal, 1.2mm); The duration was 42 minutes.

Results: Forty-five patients with refractory epilepsy received 7T-MRI (23 female, 51%; median age 28, age range 10 – 5). No side effects or interruptions were reported. Based on the radiological assessment of 3T MRI epileptogenic lesions were detected in 23/45 patients (51%). Based on 7T-MRI epileptogenic lesions were detected in 34/45 patients (76%). The diagnosis at referral was revised based on 7T-MRI in 15/45 patients (33%). In 14 pts (31%) newly detected structural epileptogenic lesions were reported (abnormal glial proliferation and/or abnormal cortical organization in 12 and migrational abnormalities in 2 cases). In one case the previously suspected MCD was interpreted as normal brain structure. The scan was confirmatory in 14 of 45 and constantly negative (non-lesional) in 16 of 45 patients.

Conclusion: Our first clinical experience suggests improved diagnostic sensitivity of 7T-MRI compared to clinical 3T-MRI and is in line with the previous reports derived from research-focused settings.

Diffusion kurtosis parameters show a higher difference between focal cortical dysplasia and healthy tissue than standard diffusion parameters

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Purpose: The goal of this study was to compare standard gaussian with non-gaussian diffusion parameters of the brain tissue in patients with focal cortical dysplasia (FCD) and elucidate differences in separability of healthy and FCD tissue based on those two sets of parameters.

Method: Diffusion MRI with at least 20 directions and two non-zero b values (1000 and 3000) was measured in 10 patients with diagnosed FCD. FCD lesion was manually outlined in structural MRI by a skilled radiologist. Diffusion MRI data were preprocessed using a combination of FSL and MRtrix tools. Parameters of both gaussian (fraction anisotropy and mean diffusivity) and non-gaussian (mean kurtosis and kurtosis anisotropy) diffusion were calculated by Diffusion Kurtosis Estimator software. Histograms of calculated parameters inside FCD lesion and in the corresponding contralateral region were calculated and compared using chi-square histogram distance. Higher histogram distance indicates higher variations between healthy and FCD tissue in the corresponding parameter.

Results: In all patients, non-gaussian diffusion parameters in the comparison with the gaussian ones had significantly higher histogram distances. Mean kurtosis has in average five times higher histogram distance than mean diffusivity and kurtosis anisotropy 3.5 times higher than fraction anisotropy.

Conclusion: In this study, a higher difference between FCD and healthy brain tissue was observed in the case of non-gaussian diffusion parameters (kurtosis) of the brain tissue than standard gaussian ones. This suggests possible higher sensitivity of kurtosis parameters for further detection or segmentation of FCD tissue.
EEG markers for long-term, ambulatory monitoring of absences

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Purpose: Cognitive impact of absences in childhood absence epilepsy (CAE) is currently probed by long-term video-EEG monitoring with simultaneous neuropsychological testing, being time-consuming and a burden for the children and their families. Our goal is to evaluate novel absence detection methods suitable for home-based EEG recordings, to ultimately determine cognitive seizure burden and to evaluate treatment response.

Methods: We recorded four absences in three children with CAE using cEEGrids (http://ceegrid.com/). ASSYST was used to identify the number and duration of spike-and-wave discharge (SWD) trains in two out of three patients (Casillas-Espinosa PM et al. Epilepsia 2019;60:783-791.). The bi-hemispheric synchrony of the onset of the SWDs in the 0.5-4 Hz frequency band, obtained by computing the mean phase coherence (MPC) of homologues signals (Mormann et al. Physica D: Nonlinear Phenomena 2000;144:358-369.) was additionally evaluated.

Results: ASSYST detected all three SWD trains, in the bilateral pair of cEEGrid channels exhibiting the least artifacts, without false positives (FPs) or false negatives (FNs). Similarly, a substantial MPC increase, i.e. a post-onset deviation of more than two times the SD, indicated the SWDs without FPs, but one FN in a recording with excessive artifacts. We are still in the process of patient selection and collecting more absences.

Conclusion: The mobile EEG set-up using the cEEGrids containing a limited number of electrodes (10 behind each ear), combined with ASSYST, allows detection of SWD trains. The substantial MPC increase up till a maximum indicates that in all cEEGrid signals synchronous behavior arises approximately 500ms after the onset of the SWDs. A next step is to study whether the bi-hemispheric synchrony can be used as measure to identify those SWD trains which are related to impaired consciousness.

Understanding BOLD signal variability in paediatric epilepsy

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Purpose: Greater variability of neuronal signalling, measured as the standard deviation of the blood oxygen dependent signal (BOLD_{SD}), relates to information processing capacity. Conversely, aberrant BOLD_{SD} may underlie certain neurodevelopmental disorders. Here, resting-state functional magnetic resonance imaging (rs-fMRI) was used to determine differences in BOLD_{SD} between children with and without epilepsy. We hypothesized that changes in neural processing due to epilepsy lead to measurable variations in BOLD_{SD} patterns, and that these could serve as biomarkers of regional functional integrity.

Methods: We studied 24 controls (12 females, mean age 8.52 ± 1.35 years) and 18 patients (10 females, mean age 11.5 ± 3.4 years) with medically refractory epilepsy that underwent imaging for preoperative planning. In addition to T1-weighted scans, rs-fMRIs were acquired while the children were watching a 5-minute animated movie. Standard preprocessing steps (FSL v6.0, FMRIB) were followed. For each subject, the functional data was divided in 8 blocks, and the standard deviation of the normalized mean of the blocks was used to obtain BOLD_{SD} values for each brain region (n = 90) as defined by AAL atlas. Whole-brain two sample t-tests were used for group comparisons and significance was set at p <0.05 FDR-corrected.

Results: Children with epilepsy showed significantly lower BOLD_{SD} in left inferior and middle temporal gyri (p < 0.001), right caudate nucleus (p < 0.01), cuneus (p < 0.001), and fusiform gyrus (p < 0.001), and significantly increased BOLD_{SD} bilaterally in inferior occipital gyri (p < 0.0001). There were no significant differences when comparing whole-brain BOLD_{SD} values.

Conclusions: Neuroplastic changes in epilepsy may depend on an optimal amount of internal neural variability driven by the identified key regions. Certain temporal and occipital regions may underlie neural processing differences in children with epilepsy. Further studies may correlate these findings with behavioural testing.
Dynamic segregation and integration during interictal epileptic discharges revealed by connectome spectrum analyses

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Purpose: Brain networks are characterized by complex interactions of segregation and integration that can be altered in epilepsy. Here we measured the dynamic interplay between segregation and integration regimes during interictal epileptic discharge (IEDs) in patients with temporal lobe epilepsy (TLE) using graph signal processing, a decomposition of the EEG signal on the structural connectome (SC).

Methods: High-density EEG was recorded in 11 TLE patients. IEDs were marked and aligned at the center of epochs of 1 second. The activity of 118 brain regions was estimated using an individual headmodel and distributed inverse solution. Using a template SC, the source signals were graph-signal processed: they were decomposed as the sum of SC graph Laplacian eigenvectors, or ‘network structural harmonics’. For each subject, the energy spectrum of the transformed signal was split into two: the low-frequency harmonics (LF, long-range interactions reflecting network integration) and the high-frequency ones (HF, short-range interactions reflecting segregation). The first were used to reconstruct the part of the ROI traces mostly coupled to the underlying structure (Xc), while the latter the decoupled one (Xd). Xc and Xd norms were calculated over all brain regions and the dynamics of their energy distribution along the IED were compared with a cluster-based permutation test across patients.

Results: Two significant clusters were identified, corresponding to the IED onset and its first peak. Between the start and the midrise time-point, the content of HF harmonics was significantly bigger than LF (p<.05). Around the IED peak instead, the energy of the coupled signal was the predominant one (p<.05).

Conclusions: Our results suggest a temporal succession of segregation and integration regimes during IED. The initially increased segregation could reflect the spatially confined nature of the IED onset, while the later increased integration could reflect propagation as an effective information transfer to the epileptic network.

Detecting electrical discharges using MRI: insights to the neuronal current Imaging sequence and results in patients with first unprovoked epileptic seizure

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The fundamentals of the diagnosis of a first unwitnessed epileptic seizure rely on the evaluation of a patient’s history. However, history is sometimes conflicting and frequently not available. Hence, objective biomarkers to prove, that a patient suffered a seizure, are of highest practical relevance. Standard EEGs, especially in the ambulatory setting, lack interictal epileptiform discharges, therefore a negative EEG does not exclude an epileptic seizure nor epilepsy. In the previous years, many investigations have been made to investigate, if high frequency oscillations (HFO) can be used to localize the seizure onset zone. Could detecting HFOs also help to determine, if a patient had an epileptic seizure? And if they are present, do they predict the risk for subsequent seizures? HFOs are only detectable using intracranial electrodes, and therefore not available in patients after a first possible seizure. MRI is a noninvasive diagnostic instrument with widespread clinical availability. The stimulus-induced rotary saturation method can potentially detect HFOs in deeper brain structures with the high spatial resolution of the MRI. Its contrast is based on the resonance effects between the magnetization locked by a spin locking pulse and an oscillating magnetic field induced by neuronal activity. The effect has repeatedly be shown in phantom experiments. We are evaluating the potential of this novel imaging techniques in a prospectively collected cohort of first seizure patients (the SWISS FIRST study) with patients undergoing diagnostics after a potential first epileptic seizure and in patients undergoing phase II evaluations due to refractory epilepsy.

Preliminary results with patients from the Swiss First cohort indicate a sensitivity of 51.4% using the NCI sequence, compared to a sensitivity of 5.4% of interictal EEG. Whether a NCI signal can predict the outcome of a patient, the seizure recurrence rate, will be assessed after an observation period of two years.
Delphos 2.0: detecting and tracking the fine temporal dynamics of oscillations in intracranial EEG

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**Purpose:** Delphos, which stands for Detector of Electrophysiological Oscillations and Spikes, has been designed to detect both epileptic spikes and oscillations in intracranial EEG. It is based on analytic wavelet transform and robust time-frequency normalisation. This program has been shown to be precise and sensitive, and relevant for clinical application. Here, we present the recent improvements of the software.

**Methods:** First, wavelet ridge, which corresponds to the local maxima along the frequency axis of a given oscillation, permits to track the frequency modulation of the oscillations. These ridges are used to estimate the duration, number of periods and frequency of the oscillations. This technique has been compared to original Delphos (1.0) on the HFO detector benchmark from Roehri et al. 2017 Plos ONE. Moreover, we added a sanity check using the Kullback-Leibler divergence to control whether the time-frequency normalisation was done correctly. Finally, we made an open-access plugin of Delphos callable within the AnyWave software and an independent program callable with command line.

**Results:** The results of the benchmark showed increase sensitivity over Delphos 1.0 as Delphos 1.0 misses some frequency-modulated oscillations. Importantly, the increase in sensitivity is not achieved at the expense if the precision as the precision of the new algorithm is similar to the original one. Secondly, we showed examples were the sanity check based on the Kullback-Leibler divergence highlights frequency bands where the normalisation did not perform correctly because of the presence of power line artefact or semi-continuous oscillations. Finally, we illustrated implementation of Delphos in AnyWave and how the detections are labelled over the SEEG traces.

**Conclusion:** With these improvements and the release of an open-access version of Delphos (available at: https://meg.univ-amu.fr/wiki/AnyWave:Plug-ins), we wish to push forward the clinical application of oscillations characterisation in epilepsy and sleep research.


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**Purpose:** In patients with drug-resistant temporal lobe epilepsy (TLE) anterior temporal lobe resection (ATLR) should be considered as an alternative treatment option. A significant postoperative complication is language impairment. Reading involves various aspects of language function. We studied the neural correlates of reading in TLE patients before and after ATLR using functional MRI (fMRI).

**Method:** Forty-four patients with TLE due to hippocampal sclerosis (24 left) and 18 healthy controls were included in this study. All patients performed a reading functional MRI task preoperatively and 4 months following ATLR. Preprocessing and activation analysis were performed with statistical parametric mapping. Connectivity analysis was performed with network-based statistic.

**Results:** Preoperatively, in left TLE (rTLE) left lateralized activations were seen in the middle temporal gyrus (MTG) and the inferior frontal gyrus (IFG). In right TLE (rTLE), bilateral activations were observed in the MTG, and only left-sided activations were detected in the left IFG. Postoperatively, bilateral activations were seen in the MTG in ITLE. Only left-sided activations in the MTG, STG and IFG were detected in rTLE following ATLR.

In ITLE, connectivity analysis revealed widespread decreased frontotemporal connectivity with the ipsilateral and to the contralateral hemisphere preoperatively compared to postoperatively. In rTLE, we observed decreased ipsilateral and contralateral connectivity as well but to a lesser extent. Postoperatively compared to preoperatively an increase in connectivity, mainly ipsilateral, was detected in ITLE whereas in rTLE these results were not significant.

**Conclusion:** Preoperatively, left and right TLE patients recruited predominantly left frontal and temporal areas when reading sentences. Postoperatively, reading also involved homotopic areas within the right hemisphere in ITLE, highlighting the importance of contralateral language networks supporting reading function. Furthermore, connectivity analysis revealed increased connectivity within the ipsilateral fronto-temporal language network following left ATLR suggesting a normalization of language networks as soon as the epileptogenic focus is removed.
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Functional reorganization of language networks after temporal lobe resection

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Purpose: In patients with intractable temporal lobe epilepsy (TLE), anterior temporal lobe resection (ATLR) is a viable treatment option to control seizures. However, ATLR may impair language function. In this work, we utilized functional magnetic resonance imaging (fMRI) to evaluate the functional language connectome in TLE patients before and after left or right ATL. We examined whether functional connectivity may predict language decline following ATL.

Method: We studied 44 patients with unilateral medial TLE due to unilateral hippocampal sclerosis (24 left) and 18 healthy controls on a 3T MRI scanner. All subjects performed language fMRI (verbal fluency) and neuropsychological testing (verbal fluency, naming) preoperatively and again four months after ATLR. Connectome analysis was based on 50 cortical language-related and 4 hippocampal regions of interest (ROIs). Network-based statistics was used to analyze differences in connectivity, compare pre- and postoperative data for left and right TLE individually, and perform regression analysis between the preoperative language connectome and neuropsychological test results.

Results: For both left and right TLE, a significantly reduced connectivity structure (p < 0.0001) was observed after ATLR. Left TLE showed primarily impaired connectivity for the left and right inferior frontal cortex (IFC) and both temporal lobes, while right TLE showed alterations particularly for the right IFC. Left TLE showed increased fronto-temporal connectivity within left and right hemisphere and within the right IFC. Right TLE showed a widespread increase in connectivity especially for the right IFC to ipsi- and contralateral regions. In left TLE, greater posterior hippocampal connectivity was related to better naming ability, and a higher integration of contralateral language ROIs was significantly related to less postoperative decline in naming.

Conclusion: The critical role of the left hippocampus during language tasks is emphasized by widespread disruptions primarily observed in left TLE. Postoperative reorganization hints at multiple systems supporting language function.

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Brain morphometry from post-contrast MRI to analyze data from first-seizure patients acquired with clinical protocols

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Purpose: Brain morphometry is usually derived from high-resolution, native T1-weighted (T1w) MRI. However, such dedicated protocols are sometimes missing in imaging data from patients acquired in clinical routine, but instead, a T1w image with a contrast agent is available. Existing morphometry tools like FreeSurfer yield unreliable results when applied to post-contrast images or might even fail completely. Consequently, these acquisitions are often excluded from morphometry studies, which reduces the sample size. We hypothesize that deep learning-based morphometry methods can extract morphometric measures also from post-contrast images.

Method: We have extended DL+DiReCT, an in-house developed morphometry tool using deep-learning (DL), to cope with post-contrast MRI. Training data were enriched with imaging data where both native and post-contrast images from the same session were available. Both images were coregistered and morphometry derived from the native image with FreeSurfer was used as ground truth for the post-contrast image. Global and regional cortical thickness derived from native and post-contrast images were contrasted to results from FreeSurfer. The method was trained on non-epileptic patients and subsequently applied to a single-center subgroup of first-seizure patients enrolled in a prospective study (The Swiss-First study).

Results: In the non-epileptic patients, correlation coefficients of global mean cortical thickness between native and post-contrast images were significantly higher with DL+DiReCT (r=0.91) than with FreeSurfer (r=0.75). On preliminary data from first-seizure patients, 76 had both a native and post-contrast MRI where the high correlation could be confirmed (r=0.90). From additional 49 patients of the study only post-contrast MRI were available which would otherwise not be accessible for morphometric analysis. Using the proposed method, the study sample size could be increased by 56%.

Conclusion: Brain morphometry can be derived reliably from post-contrast images using DL-based morphometry tools, allowing the inclusion of routinely acquired incomplete datasets for analysis and potential future diagnostic morphometry tools.
Anatomical and functional alterations in juvenile myoclonic epilepsy: voxel-based morphometry and resting-state fMRI study

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Purpose: We aimed to investigate the structural and functional brain abnormalities in juvenile myoclonic epilepsy (JME) patients with photosensitivity.

Method: Thirty JME patients, 15 of (50%) who were photosensitive (JME-PS) and 32 healthy controls (HC) were involved in the study. The high-resolution T1-weighted MRI data were acquired for voxel-based morphometry (VBM) analysis, and resting-state functional MRI data were acquired for functional connectivity (FC) analysis. The regions that showed significant differences in VBM analyses, were used as regions of interest in FC analysis for the comparisons between the whole JME group, which consist of PS and non-photosensitive (NPS) JME subgroups, and HCs. Cluster-level significance was set at family-wise-error (FWE) corrected p < 0.05.

Results: The left postcentral gyrus showed decreased connectivity in the right dominant bilateral middle cingulate gyrus, the right dominant bilateral supplementary motor area, and right superior frontal gyrus whereas left cerebellum crus 1 showed decreased connectivity in right cerebellum lobule IX and dorsal pons in JME-PS compared to the HCs (pFWE-corr=0.0014, pFWE-corr=0.0436, respectively). The left middle temporal gyrus showed decreased connectivity with the left dominant bilateral superior frontal gyrus in JME-PS compared to JME-NPS (pFWE-corr=0.0016). Left precentral gyrus showed; i) increased connectivity with left superior frontal gyrus in JME-NPS compared to HCs (pFWE-corr=0.0015), ii) decreased connectivity with right dominant bilateral calcarine fissure and occipital pole in JME-PS compared to JME-NPS (pFWE-corr=0.0103).

Conclusion: This study revealed structural abnormalities of the cerebellum, temporal gyrus, and parietal lobe besides the frontal areas and abnormalities in the FC of these areas with key structures for the pathogenesis of photosensitivity. Our results reinforce the existence of functional-anatomic ictogenic networks in JME and the concept of ‘system epilepsies’.

Network characterization of the prefrontal cortex in children with intractable epilepsy

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Purpose: Children with intractable epilepsy often display executive dysfunction independent of their epileptic onset zone. In addition to poor performance on executive functioning (EF) assessments compared to healthy children, neuronal dysregulation has also been observed. These studies have revealed that children with epilepsy show non-typical patterns of neuronal activation relative to controls in areas involved with EF (Gutierrez-Colina AM. Brain Imaging Behav. 2021). Given the known importance of the prefrontal cortex (PFC) in EF, the current study aims to characterize the activation of various regions within the PFC in children with intractable epilepsy, compared to controls.

Method: Pediatric patients with intractable epilepsy, and age/sex matched healthy controls, underwent structural and resting-state functional MRI. Functional connectivity of various brain regions in the PFC were characterized using graph analysis. Independent sample t-tests were performed to assess differences in network metrics between healthy controls and patients.

Results: Ten patients and ten controls completed the study (12 females, age M=9.93 years, SD=3.64 years). Participation of the left inferior frontal gyrus was reduced in patients with epilepsy compared to controls (p=0.0188). Predominantly significant differences between patients and controls were found for the clustering coefficient where various bilateral regions including the precentral gyrus, inferior frontal gyrus (both p<0.01) and superior frontal gyrus (p<0.05), were significantly lower for patients with epilepsy compared to controls.

Conclusion: This study revealed a decreased clustering coefficient in prefrontal areas associated with EF for patients with epilepsy compared to controls. The impact of the clustering coefficient has met with varied interpretations in the literature, wherein individual differences in EF have been associated with both increased and decreased clustering coefficients (For a review, see Reineberg AE. Hum Brain Mapp. 2016). To fully elucidate the impact on patients, EF assessments should be considered as per the current analysis.
Assessing and predicting visual outcomes after anterior temporal lobectomy and selective amygdalohippocampectomy – a quantitative comparison of clinical and tractography data

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Purpose: Anterior temporal lobectomy (ATL) and selective amygdalohippocampectomy (SAHE) are effective treatment strategies for intractable temporal lobe epilepsy but may result in a contralateral superior visual field deficit (VFD). VFDs following epilepsy surgery are caused by intraoperative damage the optic radiation (OR). This imaging study aimed to predict and compare visual outcomes using diffusion based connectomes.

Methods: We studied 62 TLE patients who underwent ATL (n=32) or SAHE (n=30). Incidence rates of VFDs (n=44) and quantitative perimetry outcomes (n=43) were compared between treatment groups. Whole Brain Connectomes were calculated using MRTrix3 and tracts were extracted from standardized atlas regions. Results were warped onto postoperative T1w images and OR damages determined by measuring the volume overlap with the resection zone. Volumetric tract damages were correlated to perimetry results (n=36). Furthermore, Fixel-Based-Analysis was performed (n=36) to assess group differences in terms of microstructural changes within the OR.

Results: Altogether, 56% of all patients had postoperative VFDs (78.9% after ATL, 36.36% after SAHE, p=0.011). VFDs and OR damage tend to be more severe within the ATL group as compared to SAHE patients (mean defect -3.99 db vs. -1.36 db, p=0.007; OR damage 69.2 mm3 vs. 3.8 mm3, p=0.002). OR damages were able to predict postoperative VFDs with a sensitivity of 86% and a specificity of 78%; these rates did not differ between treatment groups. A linear-regression model with OR damage as dependent variable showed significant correlation with vision decline and could explain 47% of variance (R²=0.47, p=0.0001). Fixel-Based-Analysis visualized a trend towards more widespread white matter changes within the ATL group.

Conclusions: Patients undergoing ATL are at higher risk for postoperative VFDs than those undergoing SAHE. Furthermore, VFDs tend to be more severe after ATL than after SAHE. Diffusion based tractography of the OR is a feasible method to reliably predict this morbidity in both treatment groups.

The cost-effectiveness of the HARNESS MRI protocol in focal drug-resistant epilepsy in a limited-resources country: an Egyptian study

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Purpose: ILAE recommended the harmonized neuroimaging of epilepsy structural sequences (HARNESS-MRI) to improve lesion detection in patients with focal DRE. The application of this protocol is still limited in low-resources countries (LRC) mainly due to high costs. We highlight our experience in applying such protocol in the management of patients with focal DRE.

Methods: Two hundred and thirty patients diagnosed with focal DRE at the Cairo University epilepsy clinic underwent conventional MRI (C-MRI) and HARNESS-MRI. Electro-clinical data were collected. After the radiology report, MRI was reviewed in the epilepsy surgery multi-disciplinary meeting (MDM). We compared findings of C-MRI, HARNESS-MRI versus HARNESS MRI reviewing during MDM. Cost-Benefit, as well as Incremental Cost-Effectiveness Ratio (ICER) between c-MRI and HARNESS MRI protocol regarding lesion detection, was calculated.

Results: Two hundred and thirty patients with focal DRE were included. The mean age was 20 years, 148 patients were male. Epileptogenic lesions detected by c-MRI & HARNESS MRI before and after MDM were 40, 106 & 131 lesions, respectively; with p-value <0.001. Sixty-nine percent of the lesions detected by HARNESS-MRI were missed on C-MRI. The most common lesions missed on C-MRI were mesial temporal sclerosis (MTS) and cortical developmental malformations (CDM). 37 MTS and 32 CDM were detected after MDM, compared to only 6 and 3 respectively, detected on c-MRI with a p < 0.001. Analysis of AVERAGE cost per each lesion detected revealed that using C-MRI, it costed 268 $ per lesion, compared to only 193 $ per lesion in HARNESS-MRI.

Conclusion: The application of H-MRI being cost-effective is highly recommended even in limited-resource countries, for better management of patients with focal DRE.
Automatic and manual segmentation of the piriform cortex: method development and application to patients with mesial temporal lobe epilepsy

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Purpose: The piriform cortex (PC) is located at the junction of the temporal and frontal lobes and is involved physiologically in olfaction and memory. In mesial temporal lobe epilepsy (mTLE) the PC is regarded as a key node within the epileptogenic network. Its study at scale is held back by the absence of automatic methods for its segmentation on MRI. We developed a method enabling automatic segmentation of the PC in patients with mTLE.

Method: First, we validated a manual segmentation protocol for PC volumes in healthy controls. We then integrated those manually derived images into the Hammers Atlas Database (www.brain-development.org) and used an extensively validated method (MAPER) (Heckemann et al. Neuroimage 2010;51(1):221-227.) for automatic segmentation of the PC. We validated the use of automated PC volumetry against manual segmentations in MRIs of 30 healthy controls and in MRIs of 20 patients with unilateral mTLE and hippocampal sclerosis. Subsequently, PC was segmented automatically in a large mTLE patient cohort (n = 116).

Results: The manual segmentation protocol yielded PC volumes of 485 ± 78 mm³ on the right and 461 ± 106 mm³ on the left in healthy controls. Intrarater reliability was good with Jaccard overlaps (intersection/union) of ~0.7. Interrater overlap was 0.53 - 0.58. Automatic and manual segmentations overlapped with a Jaccard of ~0.5 and a mean absolute volume difference of ~22 mm³ in healthy controls and ~0.40/ ~28 mm³ in mTLE. Considering the lateralisation of hippocampal sclerosis in patients with mTLE, the ipsilateral PC was 7% smaller than the contralateral PC (489 mm³ ± 74 mm³ vs. 523 mm³ ± 65 mm³, p < 0.001).

Conclusion: PC atrophy lateralised to the side of hippocampal sclerosis in mTLE patients, supporting its involvement in epilepsy. Automated piriform cortex volumetry can now be applied at scale in healthy controls as well as in pathology.
Neuropsychology

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Cognitive features of adult focal epilepsy with unknown etiology revealed by the Montreal Cognitive Assessment

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Purpose: Focal epilepsy with unknown etiology is common in adult epilepsy in clinical practice but cognitive features of these epilepsies are poorly understood. The current study aimed to clarify cognitive features of focal epilepsy with unknown etiology.

Method: Adult patients (≥ 18 years old) with focal epilepsy without intellectual disability or any neurological or psychiatric disorders were enrolled in this study. We applied the Montreal Cognitive Assessment (MoCA-J) to evaluate cognitive performance.

We investigated associations between clinical features of epilepsy and MoCA-J scores using multiple regression analyses.

Results: Overall, 125 patients participated in this study. Longer active seizure period (β= −0.332, P < 0.001) and electroencephalography (EEG) findings of left temporal focal epileptic discharge (β = −0.213, P = 0.012) were associated with lower total MoCA-J scores. In subdomains, several clinical factors (seizure active period, age at last seizure, and number of anti-seizure medicines) were associated with MoCA-J sub-items (attention, delayed recall, and language). Similar to the total score, longer seizure active period (β = −0.32, P < 0.001) and EEG findings of left temporal focal epileptic discharge (β = −0.227, P = 0.01) were associated with lower visuospatial and executive function scores. In contrast, EEG findings of left non-temporal focal epileptic discharge were associated with higher visuospatial and executive function scores (β = 0.174, P = 0.047).

Conclusion: Some clinical features (seizure active period, age at last seizure, and number of anti-seizure medicines) are associated with cognitive impairments. The causal relationships between these factors require further investigation. Our results revealed that epileptic activity in the left temporal lobe is associated with broad cognitive impairment. In contrast, epileptic activity in the left neocortex other than temporal lobe had less influence on the right hemisphere, which plays a major role in visuospatial function.

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Strategy for inducing sleep in pediatric EEG recording: sleep deprivation and administration of melatonin with H1-antihistamine

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Purpose: Achieving stable sleep during EEG recording in children is important because it increases the yield of EEG abnormalities by reducing the amount of artifacts. We aimed to evaluate the efficacy of a combination method of sleep deprivation and use of melatonin with H1-antihistamine as an alternative sedative method instead of chloral hydrate for recording sleep EEG in children.

Method: Children who were able to cooperate the combination method were included. Parents were requested to deprive sleep their children the day before taking EEG (keep awake for at least 2 hours prior to the start of the recording in under aged 1 year; put their children to bed 2 hours after regular sleeping time and awaken at their usual time in the morning in 1-3 years age; reduce their total sleep time by 6 hours in 3-7 years age and by 4 hours in over aged 7 years group). Oral melatonin and H1-antihistamine 30 minutes before the recording were administrated. We defined adequate sleep as the appearance of sleep spindles and inadequate sleep as the need for additional chloral hydrate.

Result: A total of 189 patients were included retrospectively and the median age was 11.1 years (range 0.2-17.9). Among them, 130 patients (68.8%) took anticonvulsants and 47 patients (24.9%) had any neuropsychiatric comorbidities. Successful rate of new sedation strategy was 84.1% without any adverse events. However, 30 patients (15.9%) received additional chloral hydrate and adverse events were reported in 23.5%, including irritability and prolonged drowsiness after sedation. The adequate sleep group showed successful sleep induction in children of all ages and even in patients with neuropsychiatric problems.

Conclusion: The combination of sleep deprivation and administration of melatonin with H1-antihistamine successfully induces sleep and is safe when recording EEG.
Supporting attention in children with epilepsy (SPACE): pilot of a psychoeducational intervention for children with epilepsy and difficulties with attention

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Purpose: Children with epilepsy are at risk for impairing symptoms of ADHD especially difficulties with attention. There is limited evidence regarding the use of psychological interventions for children with epilepsy and attention difficulties. We developed and piloted a novel psychoeducational intervention for children with epilepsy and difficulties with attention.

Methods: Eligible children with epilepsy (8-13 years) and difficulties with attention underwent comprehensive psychological assessment and took part in the SPACE intervention a recently developed 6-week psychoeducational intervention. The first three sessions of SPACE took place in groups of 3-5 children and two psychologists. The final three sessions involved one psychologist meeting the child and parent. The child’s teacher joined for one of the final three sessions. The first group of participants participated in the intervention in person. Subsequent groups took part online due to COVID-19 related restrictions. Measures of ADHD -inattention symptoms (parent and teacher), executive functioning (child, parent and teacher) and epilepsy specific and general Health Related Quality of Life (HRQOL) (child and parent) were administered before and three months after completing the intervention.

Results: Twenty-seven children with epilepsy expressed an interest in participating. Sixteen children met eligibility criteria and participated in a single arm pilot of the intervention. Pre- and post-intervention data was available for 15 of the 16 children. Improvement in function was noted on all measures but only reached statistical significance for child ratings of executive functioning (p=0.030) and HRQOL (p=0.043), and parent rated child HRQOL (p<0.001).

Conclusion: Psychoeducational interventions for children with epilepsy and difficulties with attention can lead to improved executive functioning and HRQOL. They may be a useful first-line intervention for children with epilepsy at risk for, or diagnosed with ADHD and/or be used in combination with pharmacological treatment with children with epilepsy and ADHD. However, more robustly designed studies are needed.

Physical activity and cognition in epilepsy

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Objective: To assess whether regular physical activity (PA) is related to clinical and cognitive variables and quality of life (QoL) in adult people with epilepsy (PWEs).

Methods: The Habitual Physical Activity Questionnaire (HPAQ) was related to clinical and cognitive variables, as well as to the Satisfaction Scale for Physical Activity (SSPA) and the QOLIE–31 scores of this sample of PWEs, with a significance level of p<0.05.

Results: A total of 60 PWEs were included, with a mean age of 42.4±13.6 years, 50% of whom were female, 38 cases with temporal lobe epilepsy with hippocampal sclerosis, and 22 cases with other epilepsies. Longer seizures were correlated with lower levels of PA in leisure time (Pearson correlation, r= -0.276; p=0.036). The HPAQ total score was correlated with the total score (r=0.351; p=0.006), with satisfaction with the practice of walking during leisure time (r=0.334; p=0.009), and with satisfaction with the practice of moderate/vigorous physical activity (r=0.278; p=0.032) from the SSPA. The HPAQ occupational PA was correlated with perception (r=0.300; p=0.021), memory (r=0.381; p=0.003), the Semantic Verbal Fluency Test (SVF) (r=0.427; p=0.001), and the MMSE (r=0.327; p=0.012). The total HPAQ score was correlated with the SVF (r=0.336; p=0.009) and the MMSE (r=0.254; p=0.049). No correlation was found between the QOLIE–31, the HPAQ, and the SSPA.

Conclusion: The longer duration of epilepsy correlated to the lower levels of PA. Greater satisfaction with the practice of PA was related to higher levels of PA. A better cognitive performance was significantly related to regular PA. There was no relationship between QoL and the practice or satisfaction with the practice of PA, suggesting the involvement of different psychosocial aspects.
Effectiveness of learning a list of words with an emotional load compared to neutral words in patients with temporal lobe epilepsy

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Purpose: There is a large body of research reporting the relation between emotions and memory. More efficient remembering can refer to emotionally arousing pictures or events, but also to individual words with an affective tone. The described effects are related to the functional neuroanatomy of the temporal lobe, e.g. hippocampus and amygdala. The aim of the study was to evaluate the effectiveness and profile of remembering affective words in people with MTLE epilepsy.

Method: The study involved 41 patients with MTLE epilepsy (20 right-sided and 21 left-sided) and 40 healthy, demographically matched volunteers. The stimulus material consisted of 18 words to remember (6 neutral, 6 positive and 6 negative) presented in a random order. Affective words were taken from the Nencki Affective Word List. Patients had 5 attempts to learn a word list, and then were asked to recall them from memory after a 20-minute break. The patients also completed BDI-II questionnaire of depression, MoCA general cognitive functioning scale and the SIE-T emotional recognition test.

Results: In the group of healthy people, a significantly higher level of remembering affective words, both positive (p <0.05) and negative (p <0.001), was obtained. This effect has not been observed in patients with epilepsy. Regardless of the type of words, people with epilepsy scored lower than healthy subjects. The number of remembered negative words correlated with BDI-II scores in both groups. Overall cognitive performance (MoCA) correlated with the overall memory score, but only in the MTLE group. The SIE-T results correlated with the number of memorized affective words in the group of people with epilepsy.

Conclusion: Anomalies concerning the work of the limbic system in people with MTLE cause a different reactivity to the emotional load of words than in healthy people. More research is needed to better understand this phenomenon.

Attention impairments in temporal lobe epilepsy - the profile of patients functioning and analysis of clinical variables impact

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Purpose: In recent years, the attention and executive functions in patients with temporal lobe epilepsy (TLE) have been studied, taking into account the effects of epilepsy on the entire brain network. Most of the previous studies on attention impairment concern the pediatric population, therefore the aim of this study was to obtain information on the functioning of adult patients in this area.

Method: Twenty-five patients with TLE and twenty-five demographically matched healthy volunteers were tested with a set of neuropsychological tests to assess general cognitive functioning (MoCA) and attention: CTT, Symbol Span – subtest of WMS-IV, Visual Elevator - subtest of TEA.

Results: TLE patients achieved significantly lower scores in the MoCA test (p = 0.000) compared with controls. They also needed significantly more time (p = 0.000) in the second part of CTT. Moreover, statistically significant differences were also found in the Symbol Span scores (p = 0.002) and Visual Elevator accuracy scores (p = 0.009). A negative correlation was found between the time of suffering from epilepsy and the results of Symbol Span (p = 0.015) and Visual Elevator (p = 0.047). Additionally, age of onset of epilepsy positively correlated with the number of errors in the second part of CTT (p = 0.009). In contrast, the average number of seizures had no clear effect on the tests results. Patients were also compared taking into account the lateralization of the epileptic focus. It turned out that people with a focus in the right hemisphere presented a lower performance of the Symbol Span task (p = 0.035) and had a longer working time on Visual Elevator test (p = 0.012).

Conclusions: Patients with TLE exhibit wide ranges of attention deficits. That may affect other cognitive functions and the patients’ daily overall functioning and also explain the difficulties they may be experiencing.
Cognitive function and the longitudinal hippocampal axis in mesial temporal lobe epilepsy

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**Purpose:** Memory processing may differ along the hippocampus (HF) long axis. We tested the hypothesis that delayed visual memory deficits are associated with posterior, and delayed verbal with anterior HF atrophy in patients with mesial temporal lobe epilepsy.

**Methods:** Twenty-two adults completed Wechsler Memory Scale-II (Logical Memory, Verbal Paired Associates, Faces, Family Pictures) and three tesla magnetic resonance imaging. We used FreeSurfer version 6.0 to calculate HF volumes corrected using estimated total intracranial volume (eTIV), separated into head, body, and tail, and repeated measures Analysis of Variance to examine effects of hippocampal subdivision, side and seizure focus lateralization, with linear regression to test hippocampal subdivision volume effect on memory.

**Results:** There was a three-way interaction between seizure focus, HF side, hippocampal subdivision. Pairwise comparisons demonstrated smaller left hippocampal head for left compared to right foci patients. Right HF head, body, and tail were significantly smaller for right relative to left focus patients. For both groups respectively, head and tail were smaller ipsilaterally. A left hippocampal model (head, body, and tail volumes) predicted performance on Logical Memory, specifically for left tail. Left hippocampal volumes did not predict memory ability for Verbal Paired Associate, Faces, or Family Pictures. A right hippocampal model predicted memory ability for family pictures and verbal paired associates at a trend level. No right hippocampal volumes predicted outcomes on logical memory and faces.

**Conclusions:** We found material-specific right-left differences in memory processing, but limited relationships between segment volumes along the anterior-posterior access and memory, perhaps related to atrophy affecting all hippocampal segments ipsilateral to seizure foci. For some tests, there was a significant correlation with verbal and visual memory with left and right HF side respectively. Left anterior HF significantly correlated with visual memory. Our study suggests that while there may be functional differences along the HF longitudinal axis, left-right distinctions may be fluid.

Neurostimulation

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Transcranial focal cortex stimulation (FCS) using the EASEE System to treat pharmacoresistant focal epilepsy: anti-seizure efficacy in two prospective clinical trials

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**Purpose:** New neuromodulatory approaches are needed for patients with pharmacoresistant focal epilepsy. Here, we report results of a meta-analysis of two prospective, first-in-man, single-arm trials (EASEE II and PIMIDES I) on the clinical efficacy of transcranial focal cortex stimulation (FCS) with the EASEE System.

**Method:** 33 patients (18 male, age 18-75 y, mean age 34.6 y) were included in the two trials. Patients were implanted with a subgaleal Laplace-like electrode, individually placed over the region of the epileptogenic focus (temporal: 15, frontal: 9, other: 9), and connected to a pulse generator placed in the pectoral region. Stimulation was started in an unblinded fashion one month after implantation, with a combination of intermittent 100 Hz high frequency stimulation (HFS) and 20min/day DC-like stimulation (DCS). Patients participating in the PIMIDES I trial could additionally trigger HFS stimulation when ictal symptoms or signs were perceived. The meta-analysis evaluated the efficacy of stimulation as intraindividual effects on monthly seizure frequency, using a mixed-effects Poisson regression model.

**Results:** Stimulation was activated in 32 patients and performed for at least six months. The seizure frequency showed a significant decrease to 53% of the counted seizures in month 6 compared to baseline (p<0.001). The overall mean seizure frequency, evaluated on a group level, fell from 33.7/month to 17.3/month, corresponding to a 53.13 % responder rate after 6 months of stimulation (95 % CI: 34.74 - 70.91 %). Implantation-related adverse events were mild and transient and mostly consisted of local pain at the implantation site. In the stimulation period, there were no serious adverse events considered related to the neurostimulation.

**Conclusion:** Data from this meta-analysis of two unblinded, prospective trials with the EASEE System suggest that transcranial electrical stimulation of the epileptic focus is an effective and well tolerated novel treatment approach for patients with pharmacoresistant focal epilepsy.
Results of Vagal Nerve Stimulation in a cohort of difficult to treat epilepsy occurring in rare disease

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Purpose: The aim of our work is describe the outcome of difficult to treat epilepsy in a cohort of pediatric patients affected by rare disease treated with Vagal Nerve Stimulation.

Method: Retrospective inclusion criteria were: a diagnosis of genetic rare disease suspected or confirmed by genetic tests, the occurrence of difficult to treat epilepsy defined as the failure of almost two anti-epileptic drugs, the lack of major malformation of cortical development (only normal or minimal alteration in MRI studies) and a follow-up > 1 year.

Results: Among 65 patients implanted between 2007 and 2021, we collected 12 patients (5 female, 7 male) affected by rare disease implanted at the mean age of 8 years (1-14 years), having a history of difficult to treat focal or generalized epilepsy before the implant ranging from 6 months until 8 years and a mean follow up after the implant of 6 years (2-12 years).

Currently 3 out of 11 patients are seizures free, 2 out of 11 patient are in McHugh 1A scoring, 6 are in 2A and one is unchanged (class V). Regarding the patients currently seizures free, one presented with atypical absences (SRPX2 gene), one with focal seizures evolving in drop attacks (16p11.2 deletion) and one with long lasting hypotonic lateralized seizures (unknown syndrome). The unchanged patient (unknown syndrome) didn’t benefit from VNS but the reintroduction of CBZ after the implant decreased > 50% the frequency of the seizures.

Conclusions: VNS could be an option for difficult to treat epilepsy in rare disease without major malformation of cortical development. Because the lack of evidence of the appropriateness of resective surgery in these conditions, VNS could be the first option after the failure of 2 or 3 appropriate trials with anti epileptic drugs.

Insular function in blood pressure and systemic vascular resistance regulation

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Purpose: The insula is a brain area involved in the integration of viscerosensory afferences and the modulation of autonomic responses. Its role in vascular regulation is not well defined, and its characterization would help in the semiological localization of the epileptogenic zone and could be of great relevance in the understanding and prevention of sudden unexpected death in epilepsy (SUDEP). This study aims to analyze the blood pressure (BP) and systemic vascular resistance (SVR) changes after functional activation of different insular regions through direct electrical stimulation (E-stim).

Method: An observational, prospective study was conducted, including epileptic patients admitted for stereoelectroencephalographic recording. Patients with deep electrodes implanted in the insular cortex in whom high-frequency E-stim were performed were included. Patients with anatomical or electrophysiological insular abnormalities and those in whom E-stim produced epileptic discharges or subjective symptoms were excluded from the analyses. BP and SVR were recorded beat-to-beat and their variations after insular E-stim were analyzed and compared with control E-stim of cortical non-eloquent brain regions and sham stimulations.

Results: Fourteen patients were included, 5 implanted in the right insula and 9 in the left one. 115 E-stim were performed in the insular cortex (56 in the right insula and 59 in the left), 46 in control electrodes, and 12 sham stimulations. E-stim of the right insula induced a mild increase in BP and SVR (only significant in posterior right insula), whereas stimulation of the left insula produced a mild decrease in BP with no changes in SVR. The greater responses occurred in both posterior insulas. Control and sham stimulations did not induce BP or SVR changes.

Conclusion: These results suggest an interhemispheric difference in insular vascular regulatory function, with a right sympathetic and a left parasympathetic functional predominance. Seizure-related vascular fluctuations may have a role in the pathogenesis of SUDEP.
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Vagus nerve stimulation in a real-life setting: indications, results and the search for beneficial profiles in a Brazilian cohort

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Purpose: Vagus nerve stimulation (VNS) therapy is an established treatment for pharmacoresistant patients that reduces seizure frequency by at least 50% in about half of patients, but the characteristics of the patients with the best response have not yet been identified. Thus, it is important to try to identify the profile of patients who would have the best response in order to guide early indication and better patient selection.

Methods: Retrospective study evaluating vagus nerve stimulation (VNS) as adjuvant therapy for drug resistant patients with epilepsy from six epilepsy centers in Brazil. Data from 192 patients were analysed, ages between three and 69 years old and all patients had at least six months of therapy to be included.

Results: The seizure control outcomes were classified according to modified Engel classification and in general, the response rate (>50% seizure reduction) after VNS implantation was 65.6% with nine patients (4.7%) become seizure free. The univariate and multivariate analyses have shown an association of response to treatment with female gender (OR: 2.60; p=0.008), focal interictal epileptiform discharges on EEG (OR: 2.28; p=0.050), focal seizure pattern (OR: 2.25, p=0.055) and previous neurosurgery (OR: 0.41, p=0.019).

Conclusion: VNS therapy in this brazilian series of children and adults with drug resistant epilepsy showed 66.5% of response to treatment (crisis reduction >50%), independently of age. Predictive factors for better response to VNS therapy in this population were female gender, no previous neurosurgery, focal interictal epileptiform activity, and focal seizure pattern. VNS therapy should be considered both in adults and in children with drug-resistant epilepsy.

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Vagal nerve stimulation mediated perturbation alters EEG connectivity in epileptic patients: a graph theory connectivity study

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Purpose: Vagal Nerve Stimulation (VNS) is an effective treatment for patients with Drug Resistant (DR) epilepsy that are not eligible for surgery. Albeit the effectiveness of VNS has been thoroughly corroborated, little is known about how VNS works. Our aim is to leverage the quantitative Electroencephalography (qEEG) to study how the brain reacts to VNSs perturbation.

Method: Eighteen patients (n=18) affected by DR epilepsy were longitudinally enrolled in our study. High definition EEG (64 channels) was recorded during VNS stimulation, an EEG channel placed on the VNS generator allowed to detect periods of stimulation (VNS-ON), periods preceding the stimulation (VNS-OFF) and following the stimulation (post-VNS). We used qEEG analysis to assess changes in spectral activity and network connectivity (weighted phase lag index, wPLI) that characterize these conditions. Graph theory metrics were used to calculate differences in network distribution in the studied spectral bands.

Results: No differences were found in spectral activity between ON, OFF and post-VNS conditions. Graph theory instead showed consistent changes in network organization expresses by Small World Index (SWI), Betweenness Centrality (BtwC) and Global Efficiency (gE). These differences are most significant in the slow EEG bands (Delta 0,5-3 Hz, Theta 4-7 Hz) and could imply that VNS acts on the diffusion of epileptic network.

Conclusion: VNS has a significant effect, by perturbating brain network activity as assessed by qEEG connectivity.
Optimal vagus nerve stimulation and titration for patients with drug-resistant epilepsy

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Purpose: Titration of VNS requires selection of amplitude, frequency, pulse width, and duty cycle settings and has been fundamentally empiric. However, successive clinical studies and clinical experience over the past 25 years can be utilized for modeling and assess trends of clinical effectiveness for certain stimulation parameters.

Method: A de-identified database has been compiled for patients implanted with a VNS Therapy System® prior to 2018. A subset of these subjects (n=1,178) have detailed programming history information available during the first 12 months after VNS implantation and were selected for analysis. A generalized linear mixed model (GLMM) was developed to assess the programming settings associated with patient response, defined as a 50% reduction from baseline in seizure frequency. Time to the VNS output current associated with patient response and the time to patient response were evaluated via Cox regression.

Results: The GLMM associated an output current of 1.63 mA with the highest rate of patient response. The nearest available programmable settings for output current in current VNS Systems are 1.5 mA, 1.625 mA, and 1.75 mA, and this finding aligns with current manufacturer guidance on dosing. In a subset of patients that achieved this dose prior to being lost follow-up (n=995), a small proportion of patients (n=105, % =10.5) were titrated to this VNS intensity within 3 months of VNS System implantation. Most patients (n=793, % =79.6) were titrated over 6 or more months to reach a similar level. Titration within 3 months was associated with a significantly increased likelihood of response and faster time-to-response than titration that occurred over 6 or more months.

Conclusion: Using GLMM, VNS output current near 1.625 mA is associated with the highest patient response to VNS for drug-resistant epilepsy. Titration to this VNS intensity within 3 months was associated with faster time-to-response than titration completed over 6 or more months.

CORE-VNS: a prospective outcomes registry of people with drug-resistant epilepsy treated with vagus nerve stimulation therapy - full cohort demographics

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Purpose: The Comprehensive Outcomes Registry in subjects with Epilepsy treated with Vagus Nerve Stimulation (VNS) Therapy® (CORE-VNS; NCT03529045) will document the impact of VNS Therapy in the treatment of people with drug resistant epilepsy. Here, we report the baseline characteristics of patients enrolled.

Method: CORE-VNS is a prospective, multicenter, global observational study. Recruitment was open from 2018 to June 2021 at 61 sites in 15 countries. Participants are monitored for up to 60 months after VNS implantation. Baseline information collected includes age, duration of epilepsy before VNS implantation (for first implantations), epilepsy type, aetiology, and syndromic diagnoses. History of treatments, previous epilepsy surgery and number of failed antiseizure medications (ASMs), were also recorded. During follow up visits at 3, 6, 12, 24, 48, 36 and 60 months, we assess clinical outcomes including seizure frequency, maximum seizure-free duration, seizure and post-ictal severity, quality of life, quality of sleep, use of ASMs/rescue medications and healthcare utilisation.

Results: A total of 822 individuals (49.1% female) have been enrolled, 792 of whom were implanted with a VNS Therapy System. 531 (64.6%) individuals were recruited prior to first implantation and 263 (32.0%) before re-implantation. Median age at recruitment was 24.0 years (range 1- 75), with 309 (37.6%) younger than 18 years and 176 (21.4%) below 12 years. The median number of failed ASMs was 6.0 (range 2-20) and 145 (17.6%) subjects had undergone previous epilepsy surgery. In 41.0% of those recruited the underlying aetiology was unknown followed by structural (33.1%), genetic (17.0%) and infectious (6.3%) aetiologies.

Conclusion: The number and diversity of participants included in the CORE-VNS registry will allow analysis of real-world data on efficacy and safety of the most recent VNS generators. The findings can guide physicians, people with epilepsy, regulators and payers regarding the use of VNS Therapy in drug resistant epilepsy.
Vagus nerve stimulation-evoked pupillary responses in epileptic patients: dose-dependency and control stimulation study

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Purpose: Acute VNS elicits a phasic increase in Locus Coeruleus (LC) firing1, which has been linked to VNS mechanisms of action. VNS-evoked pupil dilatation was demonstrated in rats as a possible dose-dependent biomarker2. However, in humans, it remains unclear to what extent such responses may depend on the attentional/somatosensory component of the stimulation.

Methods: Pupil size was recorded upon 4 stimulation conditions: VNS at routine current output (mid), routine+0.25mA (high) and routine−0.50mA (low), plus one control stimulation, i.e. a cutaneous electrical stimulation administered over the left clavicle at intensities rated as mid-VNS. Trains of 11 s length were delivered in blocks of 6, and repeated for 3 series with pseudorandomized order. Trials were epoched from −8 s to +22 s around stimulation onset. Pupil size was measured as percent change relative to baseline. We measured peak dilation latencies, and extracted scalar values for: i) early peak dilation (between 0 and +2.5s); ii) mean pupil-dilation-response (mean PDR, mean value between +2.5s and 7.5s). Mann-Whitney U-tests were applied for comparison between conditions.

Results: We report preliminary results from 6 VNS-implanted patients. Control stimulation elicited a peak dilation with shorter latency (1.78 s) compared to mid- and high-VNS (4.39 s and 4.52 s, respectively). Control stimulation induced a significantly greater early peak dilation compared to mid-VNS (p<0.01) and low-VNS (p<0.05). No differences across VNS intensities were found in the early peak. By contrast, significantly greater mean PDR was elicited by high-VNS (+4.6%) compared to mid-VNS (+1.6%, p<0.05) and low-VNS (+1.2%, p<0.01).

Conclusions: We could reliably record dose-dependent VNS-evoked pupillary responses in epileptic patients. VNS might induce LC activation at a later stage compared to attentional early activation, which influences the early part (<2.5 s) of pupillary responses. Mean PDR was found to be graded with the administered VNS intensity.

MRI-assessed locus coeruleus integrity linked to responsiveness to vagus nerve stimulation in patients with drug-resistant epilepsy

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Purpose: Vagus Nerve Stimulation (VNS) is an adjunctive treatment for patients suffering from inoperable drug-resistant epilepsy (DRE). Norepinephrine (NE) is a neurotransmitter that has been associated with the clinical effects of VNS by preventing seizure development and by inducing long-term plastic changes that could restore a normal function of the brain circuitry. The Locus Coeruleus (LC) constitutes the main source of NE in the brain and is characterized by widely diffused projections to both cortical and subcortical structures. However, the biological requisites to become responder (i.e. ≥ 50% reduction in the frequency of seizures) to VNS are still unknown.

Methods: Using a Magnetization Transfer-weighted Turbo-FLash (MT-TFL) Magnetic Resonance Imaging (MRI) sequence to visualize the LC in-vivo, this study aimed at comparing its integrity between responders (R) and non-responders (NR) to VNS. As part of the preliminary results, 12 subjects were scanned (9 R, 3 NR). Two subjects (1 R and 1 NR) were discarded due to an excessive motion during the acquisitions leading to a bad visualization of the LC. Based on MT-TFL images, LC masks were manually drawn for each patient and the mean intensity in the LC mask was extracted and compared to a reference region to compute the LC contrast.

Results: A non-parametric Wilcoxon Mann-Whitney U-test was conducted to evaluate whether the LC contrast differs significantly between the two populations. The results reveal a significant lower LC contrast in NR (p=0.044).

Conclusion: Our preliminary results suggest that inter-individual differences in the integrity of the LC-NE system exist between R and NR and may partially explain the variability in responsiveness to VNS. Assessing LC integrity in-vivo in patients with DRE using a MT-TFL sequence could help to predict responsiveness prior to the implantation of a device and avoid unnecessary surgeries in NR to VNS.
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**Personalized multichannel transcranial direct current electrical stimulation guided by SEEG in drug resistant focal epilepsies**

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**Purpose:** Transcranial direct electrical stimulation (tDCS) is an alternative nonpharmacological treatment for patients suffering from refractory epilepsy. This non-invasive technique is applied to decrease cortical activity with two (conventional tDCS) or several electrodes (multifocal tDCS). We investigated effects of personalized multissession, SEEG-targeted multifocal tDCS on seizure frequency (SF) and scalp functional connectivity (Fc) as measured by EEG in patients with drug-resistant epilepsy.

**Method:** Ten patients suffering from focal refractory epilepsy were recruited to study therapeutic and neurophysiological effects of long-term multifocal tDCS treatment (Starstim, Neuroelectrics). Therapy consisted of three cycles (six months) where each stimulation cycle corresponded to five consecutive days where each patient received two daily multifocal personalized tDCS sessions of 20 minutes (2x20 min tDCS at 2 mA separated by 20 min off). The montages were personalized to target epileptogenic area of each patient as defined by SEEG recordings. SF after the treatment was compared with baseline. Fc changes were analysed using EEG recordings performed before and after each stimulation cycle.

**Results:** After the last tDCS session, five patients experienced a SF decrease of 50% or more compared with baseline (Responders, average SF decrease of 74%). We estimated Fc changes between cycles and across responder (R) and non-responder (NR) patients. Responders presented a decrease in Fc (p<0.05) at the third session in alpha and beta frequency bands compared to NR.

**Conclusion:** We validated the therapeutic usefulness of personalized multifocal tDCS targeting epileptic areas identified by SEEG. Moreover, we demonstrated that a decrease in SF is associated to a significant decrease of Fc after three stimulation cycles. Such results suggest that tDCS-induced functional plasticity changes may underlie the clinical outcome differences between R and NR.

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**Multicenter long-term evaluation of safety and efficacy aspects of anterior thalamic deep brain stimulation**

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**Purpose:** The international multicentre Medtronic Registry for Epilepsy (MORE) aimed to evaluate the clinical routine application of deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS) with special regard to safety, efficacy, and outcome modifiers.

**Method:** In the registry, 179 adult epilepsy patients with ANT-DBS therapy were followed up for safety, efficacy, and battery longevity. The follow-up ended after a maximum of five years or upon closure of the study observation phase in September 2019. Thus, not all patients had the option to complete the 5-year follow-up (FU).

**Results:** The median length of exposure to DBS therapy was 3.5 years, with 105, 63, and 49 patients reaching their 3-year, 4-year, and 5-year FU visits. The monthly seizure frequency gradually decreased, achieving a median reduction of -56% at 5-year FU (p<0.0001), with most pronounced effects on focal to bilateral tonic-clonic seizures (-77%, p=0.0084). At last FU, 41% had a seizure frequency reduction ≥50% and thus classified as responders. Better seizure outcomes were observed in patients without previous resective epilepsy surgery and in patients with unifocal epilepsy. Adverse events included deterioration in epilepsy or seizure frequency, severity, or seizure type (31%), memory impairment (16%), and depression (15%) as well as 5 deaths (none ANT-DBS related). Most AEs (80%) occurred within the first 2 years after implantation. Battery depletion (Activa PC) occurred on average after 45 months.

**Conclusion:** The registry provides further evidence for the safe and effective application of ANT-DBS in clinical routine practice. While clinical benefits increased over time, side effects occurred mainly during the first 2 years. The identified outcome modifiers might help to optimize patient selection and management, but require further validation.
Ictal and interictal features of local field potentials recorded from the anterior thalamic nucleus of epilepsy patients performing deep brain stimulation with the Percept™ PC system

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Purpose: Deep Brain Stimulation of the Anterior Nucleus of Thalamus (ANT-DBS) is an effective treatment in focal refractory epilepsy. However, around 26% of patients are non-responders. The analysis of ANT-Local Field Potentials (LFPs) may help to optimize the stimulation in these patients, by correlating temporal dynamics of LFPs with ictal semiology and video-electroencephalography (vEEG).

Method: Two patients with refractory focal epilepsy performed prolonged simultaneous vEEG and ANT-DBS recordings, during a 5-day period, approximately one month after bilateral ANT-DBS implantation with the Percept™ PC neurostimulator. Timestamps for sleep staging, interictal spiking and ictal patterns were performed on EEG data. LFPs were recorded in multiple available modes during both ictal and interictal periods. vEEG and Percept PC systems were first synchronized using either head tapping over the scalp (producing signal artefacts in LFPs and EEG, also visible in video; video timestamps were used to compute the delay between systems) or computing the delay between stimulation artefacts visible in both EEG and LFPs.

Results: Seizures and long interictal periods were recorded in frequency and power domain for both patients. We found that seizures tended to occur at higher LFP power values and a detecting threshold could be proposed for patient 1. For patient 2, a seizure was also recorded in the time-domain and we found that ANT LFPs spiking preceded scalp changes in ~20 seconds (concordant with hemisphere of onset). A potential multifrequency seizure biomarker was also identified. Interictal epileptiform discharges were seen on time-domain LFP channels. Sleep-wake cycles were detectable in power-domain LFP, in which changes preceded standard visual EEG staging of sleep.

Conclusions: LFP recordings with Percept™ PC neurostimulator provide valuable interictal and ictal data, which may allow early seizure detection and help setup a closed-loop adaptive system.

Tracking cortical excitability dynamics with transcranial magnetic stimulation in focal epilepsy

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Purpose: The lack of reliable biomarkers constrain epilepsy management. We assessed the potential of repeated transcranial magnetic stimulation with electromyography (TMS-EMG) to track dynamical changes in cortical excitability on a within-subject basis.

Method: We recruited people with refractory focal epilepsy who underwent video-EEG monitoring and drug tapering as part of the presurgical evaluation. We performed daily TMS-EMG measurements with additional postictal assessments 1-6 hours following seizures to assess resting motor threshold (rMT), and motor evoked potentials with single- and paired-pulse protocols. Anti-seizure medication regimens were recorded for the day before each measurement and expressed in proportion to the dosage before tapering. Additional measurements were performed in healthy controls to evaluate day-to-day rMT variability.

Results: We performed 77 (58 baseline, 19 postictal) measurements in sixteen people with focal epilepsy and 35 in seven healthy controls. Controls showed minimal day-to-day rMT variation. Withdrawal of anti-seizure medications was associated with a lower rMT without affecting motor evoked potentials of single- and paired-pulse TMS-EMG paradigms. Postictal measurements following focal to bilateral tonic-clonic seizures demonstrated unaltered rMT and increased short-interval intracortical inhibition, while measurements following focal seizures with impaired awareness showed decreased rMT’s and reduced short and long interval intracortical inhibition.

Conclusion: Serial within-subject rMT measurements yielded reproducible, stable results in healthy controls. Anti-seizure medication tapering and seizures had distinct effects on TMS-EMG excitability indices in people with epilepsy. Drug tapering decreased resting motor threshold, indicating increased overall corticospinal excitability, whereas seizures affected intracortical inhibition with contrasting effects between seizure types.
Effectiveness of personalized microburst vagus nerve stimulation (mVNS) in patients with bilateral onset tonic clonic seizures (BTCS)

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**Purpose:** VNS is a safe, effective and widely adopted anti-epileptic treatment. Stimulation parameter optimization and personalized therapy may further improve efficacy. We investigated the safety and effectiveness of the newly developed mVNS using fMRI.

**Methods:** Twelve patients (6M/6F) with BTCS were included in a prospective multicenter trial (Microburst Study NCT03446664) and underwent fMRI during a series of varying stimulation parameters, including mVNS (short stimulation intervals with high frequency stimulations up to 350 Hz). Stimulation parameters inducing the most significant changes in thalamic BOLD-signal were used to treat patients. Quality of life (QOLIE-31) and seizure severity (SSQ) were investigated.

**Results:** All patients received mVNS based on individual fMRI results. The median seizure frequency reduction of BTCSs was 41.8% and 75.2% at 9 months and 12 months respectively; median monthly BTCS count decreased from 3.4 at baseline to 1.6 at 9 months and 1.7 at 12 months. At 12 months 8/11 patients (72.7%) were responders; 6/8 were super-responders (>80% reduction) representing 54.6% of all patients. The median total SSQ scores decreased from 5.6 to 5.3 at 9 months and 4.1 at 12 months with a median decrease in AED drug load of 38.2% and 29.4% at 9 and 12 months and an effective improvement of quality of life in 6/10 (60%) patients and 4/9 (44.4%) at 9 and 12 months.

A total of 78 AEs were reported of which 68 (87%) were non serious and 7 were non-treatment-emergent. 2/3 serious AEs were related to the implantation procedure and one was stimulation/device-related resulting in treatment and study withdrawal.

**Conclusion:** In this pilot trial the novel mVNS paradigm, titrated by individual brain activation patterns, was associated with a robust reduction in seizure frequency and with improvements in seizure severity, AED drug load and quality of life. Side effects were comparable to regular VNS therapy.

Non-invasive neuromodulation for seizures and epilepsy: evidence-based literature review and clinical application

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**Purpose:** To evaluate neuromodulation/neurofeedback (NFB) as a valid and reliable treatment for people with epilepsy (PWE), given the understanding of epilepsy as a network disease (Lopes da Silva et al. In: Handbook of Clinical Neurology, 2012;107;35-62) and significant numbers of PWE with drug-resistant epilepsy (DRE).

**Method:** Analysis was carried out combining a comprehensive literature review (>130 articles from 1968-2022) with 10-year practice experience incorporating quantitative-EEG-guided NFB (QEEG-NFB) as adjunctive in evaluation and decision-making for PWE and seizures. NFB is a subtype of non-invasive neuromodulation which has a 50+ year history with >130 research, clinical, and scientific publications.

**Results:** Literature review, despite limitations due to the nature of NFB (difficulty of obtaining large-scale, double-blinded placebo-controlled randomized clinical trials [RCTs], similar to the inability to perform RCTs in the exercise physiology sciences), and extensive experience of clinicians and researchers over six decades, demonstrates a very favorable risk/benefit ratio, warranting serious consideration of this modality in daily healthcare of PWE. When guided by QEEG analysis and electromagnetic source imaging using low-resolution electromagnetic tomographic analysis (LORETA), individualized NFB training has demonstrated the ability to decrease seizures and seizure-susceptibility, add insight toward improving reported medication side effects, and result in improvements in neural functioning correlated with improved quality of life (QOL) in PWE (Morales-Quezada et al. Epilepsy & Behavior 2019;101:106570). Collective clinical experience with EEG, QEEG functional source neuroimaging, and NFB for PWE correlated with this extensive literature review, demonstrate that NFB is a clinically-valid, time-tested, viable and evidence-based modality to be considered in epilepsy management of many PWE.

**Conclusion:** NFB is a valid and reliable, evidence-based, historically-proven modality to benefit PWE, achieving improved seizure control, guiding medication decisions, and improving overall brain network dynamics. NFB is easily implemented and provides ongoing benefits and should be a significant part of the health care of PWE.
Does Val66Met polymorphism of BDNF influence clinical response to vagal nerve stimulation in subjects with drug-resistant epilepsy?

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Purpose: The mechanism of vagal nerve stimulation (VNS) in the treatment of drug-resistant epilepsy (DRE) is not completely known. It is hypothesized to act on neurotrophins, stimulating synaptic plasticity. BDNF implicates several neurophysiological processes. A non-conservative single nucleotide polymorphism (SNP), producing an amino-acid substitution (Val66Met), affects intracellular processing and secretion of BDNF, leading to impaired plasticity. (Kowiański P, et al., Cell Mol Neurobiol. 2017; Egan MF, et al., Cell. 2003). The aim of this pilot study is to verify if the presence of SNP correlates with a worse outcome of VNS.

Method: After approval by ethics committee, 34 patients (17 M, 8 F) aged between 75 and 78 yo (median age 43), with DRE, not eligible for surgical treatment, were selected. Genomic DNA was extracted from blood samples and amplified by PCR + RFLP to detect BDNF Val66Met. Mann-Whitney test was used to verify the different presence of polymorphism in responders versus non-responders.

Results: Clinical response to VNS was assessed with McHugh classification before and 1 year after VNS: 20 patients (class I and II) were responders, 14 patients (class III or more) non-responders. There is a correlation between the presence of Val66Met Polymorphism and worse clinical response (p-value 0.0046**).

Conclusions: This pilot study paves the way to the identification of Val66Met polymorphism as a marker to tailor the treatment of individual patients and correlates a worse outcome to reduced neurotrophin-induced neuronal plasticity.

Effects of vagal nerve stimulation on EEG aperiodic parameters in subjects affected by drug-resistant epilepsy

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Purpose: The antiepileptic mechanisms of Vagal Nerve Stimulation (VNS) are currently unknown: no study has analyzed the action of VNS on EEG aperiodic component, a power spectrum 1/f-like signal related to biological functions and neuronal excitation and inhibition. (Manning, et al, J Neurosci 2009; Robertson, et al., J Neurophysiol 2019)

This study aims to investigate the effect of VNS on Exponent and Offset aperiodic parameters on 64ch EEG in patients affected by drug-resistant epilepsy (DRE).

Method: 10 patients with DRE, not eligible for epilepsy surgery and without psychiatric comorbidities, were selected. Each patient underwent a 64-ch EEG in resting state before and one year after VNS implantation; clinical response was computed by McHugh’s Class.

On each trace, 20 epochs of 8 seconds (sampling rate at 1024 Hz), free of artifacts and interictal abnormalities were selected. The aperiodic parameters were computed over the entire scalp, in individual channels on each extracted epoch. The difference before and after VNS was studied with a U test with FDR correction, in responders (McHugh Class I-II) and non-responders (McHugh Class III-IV), separately.

Results: Exponent and offset showed a global decrease in responders (exponent p 0.020, offset 0.019) and an increase after VNS in non-responders (exponent p 0.003, offset 0.000); which is confirmed in single regions.

Conclusion: Despite the need of a larger sample and the limits of a scalp-derived signal, our results show that VNS acts on aperiodic EEG components differently in responders and non-responders, suggesting a possible reduction in neuronal excitability in responders. Further studies should be carried out to identify which patients will exhibit a good response to VNS, to treat only those most likely to benefit it.
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PRediction of vagal nerve stimulation EfficaCy In drug-reSistant Epilepsy (PRECISE): prospective study for pre-implantation prediction /study design

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Purpose: Vagal nerve stimulation (VNS) can be indicated in patients with drug-resistant epilepsy. In VNS therapy, the responder rate (≥ 50 % seizure reduction) is approximately 50 %. At the moment, there is not a widely-accepted possibility to predict VNS efficacy in a given patient based on pre-implantation data, which can lead to unnecessary surgery and improper allocation of financial resources. The principal aim of the PRECISE (PRediction of vagal nerve stimulation EfficaCy In drug-reSistant Epilepsy) study is to verify the predictability of VNS efficacy by analysis of pre-implantation routine EEG.

Methods: PRECISE is designed as a prospective multicentric study in which patients indicated to VNS therapy will be recruited. Patients will be classified as predicted responders vs. predicted non-responders using pre-implantation EEG analyses. After the first and the second year of the study, the real-life outcome (responder vs. non-responder) will be determined. The real-life outcome and predicted outcome will be compared in terms of accuracy, specificity, and sensitivity. In the meantime, the patients will be managed according to the best clinical practice to obtain the best therapeutic response.

Results: The primary endpoint will be the accuracy of the statistical model for prediction of response to VNS therapy in terms of responders and non-responders. The secondary endpoint will be the quantification of differences in EEG power spectra (Relative Mean Power, %) between real-life responders and real-life non-responders to VNS therapy in drug-resistant epilepsy and the sensitivity and specificity of the model.

Conclusion: The PRECISE relies on the results of our previous work, which developed a statistical classifier for VNS response (responders vs. non-responders) based on differences in EEG power spectra dynamics (Pre-X-Stim).

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Scheduled programming reduces time-to-dose and office visits in the COVID-19 pandemic

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Intro: Titrating vagus nerve stimulation (VNS) therapy to a dose that is both tolerable and efficacious often requires multiple, small increases in stimulation intensity. Recently available models of VNS therapy offer a scheduled programming feature that permits programming events to occur on a predetermined schedule, outside of typical office visits. During the COVID-19 pandemic, patient access to office visits has been limited by institutional or governmental restrictions and concerns for infection risk, and remote patient management techniques, such as scheduled programming, have gained popularity.

Methods: To examine changes in real-world feature use, a database of programming events at primarily North American centers and collected through standard post-market surveillance was examined. The full year of 2018 (the year following release of this feature) was compared to the year of 2020, from March 1st through December 31st, when COVID-19 restrictions started to become more widespread in the United States.

Results: Scheduled programming usage increased from 23.5% of all patients in 2018 to 30.5% in 2020. While frequency of feature use increased during the pandemic, the typical method of feature use did not meaningfully change. Of patients who used scheduled programming to titrate at least 1 step, the mean number of total steps titrated with this feature increased from 3.5 to 3.8 during the pandemic. Use of scheduled programming decreases the frequency of office visits required to achieve a dose, but pre-pandemic and peri-pandemic reduction in office visits in patients that used scheduled programming were not meaningfully different (-2.1 visits in 2020 vs -1.9 visits in 2018). During both time ranges, patients who experienced 3 or more scheduled programming events were more likely to achieve a target dose of 1.5 mA in less than three months.

Conclusions: These findings suggest that the scheduled programming feature can support VNS dosing and titration in situations where remote patient management is encouraged.
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Focal non-invasive deep-brain stimulation with temporal interference for the suppression of epileptic biomarkers

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Purpose: Electrical stimulation as a neuromodulation method in epilepsy has been increasingly explored and included in clinical therapy. Recently, a new method of non-invasive brain stimulation was described by Grossman et al. 2017, the temporal interference (TI). It is based on the application of two high-frequency electric fields (>1KHz) via two pairs extra-cranial electrode. The superposition generates a low-frequency stimulation envelope which allow to stimulate a deep precise brain area. The aim was to apply a high frequency stimulation (TI-HFS) on epileptic mice to evaluate the impact on the hippocampal inter-ictal activity. Then, we demonstrated the possibility to scale this technique with human cadavers.

Method: OF1 mice (n=30) were implanted with 2 pairs of cortical electrodes and one invasive into the hippocampus. Mice were rendered epileptic by kindling and a group (TI-HFS, n=12) underwent a TI stimulation at 130 Hz (f1=1300Hz, f2=1430Hz). Sham mice and low frequency stimulation 130Hz (CT-HFS) mice, for which TI-HFS was not applied, served as controls (n=18). Spikes and high frequency oscillations were quantified in all groups. To scale this technique, 7 human cadavers were implanted with 10 stereo-encephalography (SEEG) electrodes in order to record the artefact of the TI-HFS stimulation produced by 2 pairs of skin electrodes.

Results: A decrease by 2 in the number of epileptic biomarkers (spikes: p-value=0.001 and fast-ripples:p-value= 0.023) was observed compared to Sham. Also, TI-HFS decreased all the spikes' features (Amplitude, Duration and Area;p-value < 0.001).In cadavers, stimulation envelopes up to 5mV were recorded in the human hippocampus while less than 0.5mV was in the cortex.

Conclusion: These results constitute a first proof of the feasibility and efficiency of TI to reproduce results usually obtained via invasive electrodes. The data tend to show the sufficiently focal character of the induced effects and suggest promising therapeutic applications in epilepsy.

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Vagus nerve stimulation (VNS) in patients with developmental and epileptic encephalopathies (DEE)

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Purpose: To evaluate the long-term effect and tolerability of vagus nerve stimulation (VNS) in patients with developmental and epileptic encephalopathies (DEE).

Method: Long-term outcomes from a VNS-quality registry in 105 patients with DEE were compared with patients without intellectual disability (ID, n=212). The group consisted of Lennox-Gastaut (LGS; n=62), Dravet (n=16), Rett (n=9) and 18 with other syndromes. The effect was evaluated at 6, 12, 24, 36 and 60 months. The effect on different seizures types was evaluated at baseline and at last observation.

Results: Median follow-up was 88 months for patients with DEE. Total seizure burden was reduced from 156.5 to 76.7 seizures per month for patients with DEE and from 32.3 to 12.5 to patients without ID. The responder rate (≥50% seizure reduction) after 6 months and 24 months was respectively 17.7% and 35.5% for LGS, 18.8% and 31.3% for Dravet, 11.1% and 66.7% for Rett and 16.7% and 33.3% for other syndromes. The responder rate for patients without ID was significantly better at both 6 (33.5 %, p= 0.002) and 24 months (48.6%; p=0.047) compared to patients with DEE. Median reduction for drop-attacks (tonic and tonic seizures) and generalized tonic-clonic seizures was respectively 60.0% and 33.3% for LGS, 25.0% and 18.7% for Dravet, 55.6% and 70.8% for Rett, 40.0% and 34.3% for other syndromes, and 55.5% and 38.8% for patients without ID. Mean reduction for focal seizures with impaired consciousness was 40.0% for all patients with DEE and 50.0% for patients without ID.

Conclusion: VNS is a viable treatment option for patients with DEE. Drop attacks were the seizure type with best effect. There was a high retention rate at 5 years despite less effect than patients without ID, probably due to other positive effects such as increased alertness, mood as well as milder and shorter seizures.
Entropy in the prediction of efficiency of vagal nerve stimulation

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Purpose: Surgical treatment should be offered to patients with intractable epilepsy. It is known, that resective surgery is the best option to achieve seizure freedom in these patients. If no epileptogenic focus is found, the implantation of vagal nerve stimulation (VNS) should be discussed. It is a palliative method for treatment of drug-resistant epilepsy, in only around 5% of patients we can avoid seizures completely. However 50-60% of patients report more than 50% seizure reduction (responders). In our study we tried to determine responders before implantation of VNS using entropy.

Methods: We collected EEG data from 59 patients, who underwent implantation of VNS in Brno Epilepsy Center between 2005 and 2012. We chose 8 periods from 20 minutes lasting EEG records (rest, open/close eyes, photic stimulation, hyperventilation). Patients were divided into 2 groups according the postoperative outcome (24 responders and 35 non-responders). We analyzed various types of entropy in 4 frequency bands (theta, alfa, beta, gamma) and compared these types of entropy between responders and non-responders.

Results: We found statistically significant differences in entropy mostly during hyperventilation between responders and non-responders.

Conclusion: Various types of entropy seem to be a good biomarker for prediction of the efficiency of VNS. We can use entropy in pre-surgical examination to identify the patients, who will benefit from this type of treatment.

Characterising TMS-evoked EEG potentials for treatment response in people with epilepsy

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Introduction: Transcranial magnetic stimulation (TMS) combined with high-density electroencephalography (TMS/EEG) allows exploration of cortical excitability through analysis of TMS-evoked potentials (TEPs). We investigated cortical excitability in drug resistant epilepsy (DRE), defined as epilepsy resistant to adequate trials of at least 2 ASMs, drug sensitive epilepsy (DSE) and healthy controls.

We hypothesised that cortical excitability, as measured by natural frequency power band (NF), local mean field power (LMFP) and the immediate response area (IRA), would show greater differences in DRE vs healthy controls than in DSE vs healthy controls.

Methods: We conducted single pulse (<1Hz) monophasic navigated TMS/EEG with active electrodes on three healthy controls and five people with focal epilepsy (PWE). A minimum of 150 pulses were delivered to left and right premotor cortical areas. We compared NF, LMFP and IRA across all TEPs assessing for differences using Mann-Whitney U tests with p<0.05 deemed to be statistically significant.

Results: 2/5 PWE had DSE with both taking anti-seizure medication (ASM) monotherapy. The remaining 3/5 PWE had DRE, with 2 receiving ASM polytherapy. One DRE PWE was treated with ketogenic diet only.

Left premotor TEP NF was slower in PWE than in controls (median difference 18.7 Hz, P< 0.036). We observed a trend towards increased inter-hemispheric NF asymmetry in DRE vs healthy controls (median difference 12.7 Hz, P<0.071), not seen in DSE. There were no statistically significant differences in right hemisphere NF, LMFP or IRA in PWE vs controls, and DRE vs. DSE.

Conclusion: We demonstrated slower premotor NF in PWE, both DRE and DSE, than healthy controls, while other measures of excitability were similar. A trend towards increased hemispheric NF asymmetry was seen in DRE, perhaps reflecting more powerfully epileptogenic foci. TMS/EEG investigation of a larger sample size may help elucidate mechanisms of response to ASM in DSE and DRE.
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Developing a standardized mnemonic testing tool to improve periictal and post-ictal assessments of patients in the Epilepsy Monitoring Unit (EMU) at Toronto Western Hospital

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Nurses provide care to Epilepsy Monitoring Unit (EMU) patients within a mixed neurology and neurosurgery inpatient unit at Toronto Western Hospital (TWH). The unit currently does not have an efficient and standardized assessment method to comprehensively test patients during and post seizures seizures. A complex and lengthy chart is currently available for assessing patients during seizures and post seizures at the bedside. However, according to physician and nursing input, this chart is not being adequately utilized by nurses to assess for seizures in a complex and mixed medical surgical unit. Accurate and detailed assessments are critical to establish a diagnosis and to classify seizures in this patient population. The EMU at TWH has also had a high turnover among its clinical educators and nursing staff over the last three years. This turnover and the absence of a standardized assessment method may have contributed to inconsistencies in practice. Although a European consensus on testing patients ictally exists, there is still no international consensus on the comprehensive periictal testing of patients in the EMU. This paper proposes the development and use of a mnemonic based assessment tool called the “ICTAL” lanyard tool to improve the practice and efficacy of assessing patients’ cognitive, sensory, behavioral and motor functions during seizures with the goal of improving and enhancing patient care outcomes in the EMU at Toronto Western Hospital.

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Illness representation and self-management in adolescents with functional seizures

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Purpose: Adolescents with functional seizures (nonepileptic seizures attributed to stress) miss more school, experience more academic challenges, and have poorer quality of life than healthy counterparts. To understand disparities, researchers must understand adolescents’ interpretation of their condition and self-management. Illness representation (IR) is one’s interpretation of a health threat that triggers self-management actions and evaluation of self-management effectiveness. IR includes five domains: identity, timeline, consequences, cause, and control. The purpose of this qualitative study was to explore the presence of IR domains within adolescents’ descriptions of functional seizure self-management and identify potential relationship patterns with self-management strategies and perceived effectiveness.

Method: Ten adolescents (12-19 years old, 100% female, 80% White) with functional seizures from across the United States were recruited via caregiver Facebook support groups. Semi-structured interviews were conducted and recorded using Zoom, transcribed, and coded using deduction and magnitude coding according to IR domains, self-management strategies, and perceived self-management effectiveness.

Results: Out of 135 IR meaning units, most pertained to condition consequences (41), identity (39), and cause (31); far fewer related to control (15) and timeline (9). For adolescents expressing some sense of control (vs. no control), none expressed an expectation of seizure freedom, all had a proactive plan deemed effective, and 80% had a reactive plan deemed effective. For adolescents expressing no control, 25% expressed seizure freedom was possible, all had a proactive plan deemed effective, and none had a reactive plan deemed effective.

Conclusion: Too few adolescents expressed understanding potential seizure freedom. A potential relationship pattern between controllability and use of effective reactive strategies was noted. These study findings suggest adolescents require greater understanding of condition timeline and control, which may improve self-management and perceived effectiveness. Knowledge gained will inform future functional seizure self-management surveys and interventions for improved academic, health, and quality of life outcomes.

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Paediatric Epileptology

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The European Reference Network for Rare and Complex Epilepsies, ERN EpiCARE: a cross-border collaboration towards improved care pathways

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Purpose: Present our experience in constructing a cross-border network for rare and complex epilepsies at the service of care and research, funded by the European Commission.

Methods: In 2011, the European Parliament approved a declaration that called “to prioritise epilepsy as a major disease that imposes a significant burden across Europe and take initiatives to encourage Member States to ensure equally quality in public healthcare for people with epilepsy...”). Drawing on the richness of their experience with these networks, a group of EU-based leaders, supported by the ILAE, developed an evidence-based argumentation on the reasons to create a stand-alone ERN for rare and complex epilepsies.

Results: Today, the ERN EpiCARE is composed of 50 full and affiliated HCP members and several collaborating partners. We use a referral system for patients and share medical results in a secure platform developed by the EU, aiming to ensure the same level of access to healthcare across Europe: the patient does not need to travel, the information does. EpiCARE members share, compile and assess best practices, disseminate them in the form of publications, clinical guidelines and protocols. The core actions are developed with the contribution of working groups, and the Research Council facilitates involvement of the network in collaborative research projects. We foster cooperation between different actors: universities; hospitals; patient associations; EU and international scientific societies; cross-ERNs working groups; EU member states. We contribute to education and training by organizing workshops, webinars, and by developing practical tools, targeting physicians, associations, families and patients.

Conclusions: We believe that the ERNs are the future of care, research and education in rare diseases, bringing major improvement and pavement of solutions for patients. In 2022, the ERNs budget have been renewed and increased, proof of the EU strategy to improve care for rare diseases affecting 30 million Europeans.

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Clinical and videoelectroencephalographic findings in children older than 2 years with daily Epileptic spasms

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Purpose: Late-onset spasms (LOS) are epileptic spasms starting after the first year of life. Our aim was to assess the electroclinical features and response to treatment of patients with refractory epileptic spasms (ES) that persisted after two years old and to analyze the differences between patients that presented the first ES before and after the first year of life.

Method: We retrospectively included 18 patients older than two years with symptomatic refractory epilepsy with ictal ES monitored with Video electroencephalography monitoring between 2018 and 2021. Clinical and videoelectroencephalographic findings were collected. Vineland scale was used to evaluate the neuropsychological outcome.

Results: Patients had a median age of 7 years (2-22yrs.). 78% had a structural etiology, mostly secondary to perinatal hypoxic ischemic encephalopathy and 22% malformations of cortical development (MCDs). All patients exhibited neurological deterioration and had refractory epilepsy with daily epileptic spasms. Intercital EEG showed a slow and disorganized background in all cases except for one patient with LOS. Most had multiple seizure types which included tonic, focal and atypical absence seizures, except for 3 that presented only epileptic spasms. Both groups persisted with daily seizures and had a similar response to anti-seizure medication, CBD and ketogenic diet. 11 (61%) patients had LOS. All the patients with MCD presented LOS. The ES were asymmetric in 27% of the patients, with no difference between the groups, but occurred more frequently in clusters in the LOS group.

Conclusion: Epileptic spasms may appear after the age of one. They are more frequently observed in patients with developmental and epileptic encephalopathy with an overall unfavorable cognitive outcome. In this sample of 18 patients with daily seizures we observed that patients with MCD had LOS. Other clinical, ictal semiology or cognitive and epileptic outcomes were unrelated to the age of ES onset.
De Novo“ seizures in convulsive status epilepticus in children and in those with pre-existing seizures: clinical evolution

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Introduction: Status epilepticus (SE) is the most common neurological disorder in children, being a condition resulting from the loss of the mechanisms responsible for ending convulsive access or from the initiation of mechanisms that cause an abnormal convulsive response. The aim of the present study is an analysis of the evolutionary course of SE among children with „de novo“ seizures and previously pre-established epilepsy, by studying the type of seizures, the EEG route and analyzing of the serum concentration of the antiepileptic remedies for SE prophylaxis in children.

Material and methods: A retrospective study, conducted by a single center, during the years 2015-2019. We included in the study 115 children with convulsive SE, aged between 1 month and 18 years, admitted to the Pediatric Intensive Care Unit of the IMSP Institute of Mother and Child. We analyzed the medical records to obtain variables related to demographic data and the types of crisis.

Results: From the total of 115 children with SE, 72 (62.6%) were previously diagnosed with stable epilepsy. Focal seizures were present in 32.1% of cases, and 33.04% required intubation; the mortality incidence was 3.4%. In children with previously established diagnosis of epilepsy, a pathological EEG was encountered more frequently (p <0.001). In 81% of children with pre-existing seizures, the levels of AED were known, but 51.6% of them had sub-therapeutic levels.

Conclusions: The most common SE-associated disorder was stable epilepsy. Intubation has been used mainly in patients with focal seizures. Serum subtherapeutic concentrations of antiepileptic remedies have been established more frequently in children with SE previously diagnosed with epilepsy.

Enterovirus infection prior to developing febrile infection-related epilepsy syndrome (FIRES) with some features of secondary hemophagocytic lymphohistiocytosis - a case report

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Purpose: Identifying enterovirus (EV) infection as a non-specific illness prior to developing FIRES.

Method: Review of clinical chart.

Results: A 15-year old previously well boy had a non-specific febrile illness with cough, who 6 days later developed increasing frequent partial seizures with loss of awareness. A day later, he presented to our hospital with febrile convulsive status epilepticus. An urgent MRI brain was normal. Cerebrospinal fluid(CSF) examination showed pleocytosis (WBC 130, RBC 10; lymphocytic predominance) but the FilmArray(R) meningitis/encephalitis PCR panel was negative. However, throat and rectal swabs returned positive for EV on day 3 of admission. With a probable diagnosis of EV encephalitis, he was treated with intravenous immunoglobulin for 5 days. Despite multiple anti-seizure medications (midazolam infusion, phenobarbitone, phenytoin, levetiracetam and clobazam) achieving intermittent burst suppression coma, he remained in super-refractory status epilepticus with frequent multi-focal seizures recorded during continuous EEG monitoring. Ketogenic diet was introduced on day 9 with progressively higher ratios but, no response. His autoimmune encephalopathy panel and further infection screen returned negative. He subsequently demonstrated evidence of multi-systemic inflammation with hepatic transaminitis and generalised maculopapular rash. There were other features of hemophagocytic lymphohistiocytosis with persistent fever, splenomegaly, raised ferritin at 1175ug/L, and low NK cell activity. He had decreasing white cell counts (though not reaching criteria), with normal fibrinogen and triglyceride levels. At day 15, he was given intravenous methylprednisolone pulse for 5 days, with no benefit at the end of the course. Thus, anakinra was started with clear clinical and biochemical improvement within 2 days. His CSF cytokine panel subsequently returned with raised IP10 (CXCL10), IL-6 and IL-8, which are consistent with other reports on FIRES.

Conclusion: Previous studies on FIRES had not identified any clear aetiological triggers. Our report suggests that EV infection could be a potential trigger.
Scalp HFO rates decrease after successful epilepsy surgery and are not impacted by the skull defect resulting from craniotomy

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Purpose: Epilepsy surgery can achieve seizure freedom in selected pediatric candidates, but reliable postsurgical predictors of seizure freedom are missing. High frequency oscillations (HFO) in scalp EEG are a new and promising biomarker of treatment response. However, it is unclear if the skull defect resulting from craniotomy interferes with HFO detection in postsurgical recordings.

Methods: We considered 14 children with focal lesional epilepsy who underwent presurgical evaluation, epilepsy surgery, and postsurgical follow-up of ≥1 year. We reconstructed the craniotomy and identified the nearest EEG electrodes to the skull defect in the postsurgical MRI. We applied a previously validated automated HFO detector to determine HFO rates in presurgical and postsurgical EEG.

Results: Overall, HFO rates showed a positive correlation with seizure frequency (p<0.001). HFO rates in channels over the HFO area decreased following successful epilepsy surgery, irrespective of their proximity to the skull defect (p=0.005). HFO rates in channels outside the HFO area but near the skull defect showed no increase following surgery (p=0.091) and did not differ from the HFO rates of their contralateral channels (p=0.726).

Conclusion: Our observations show that the skull defect resulting from craniotomy does not interfere with postsurgical HFO detection. This supports the notion that scalp HFO can predict postsurgical seizure freedom and thus guide therapy management in focal lesional epilepsy.

Diagnostic performance of a blood test for the early, simple and fast detection of Glut1 deficiency syndrome

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Purpose: GLUT1 deficiency syndrome (Glut1DS) is a genetic neurometabolic disease that causes a wide range of neurological symptoms, in children and adults – epilepsy, cognitive impairment, permanent or paroxysmal movement disorders, either combined or in isolation. Glut1DS is a treatable disorder. However, its diagnosis relies on an invasive test, i.e., a lumbar puncture (LP) to measure glycorrhachia, and, sometimes complex, molecular analyses of the SLC2A1 gene. This procedure limits the number of patients able to receive the standard of care. METAglut1™ is a simple blood test that quantifies GLUT1 at the red blood cell surface.

Method: We performed a multicenter validation study in France, involving 33 centers. We studied two patient cohorts: a prospective cohort, consisting of patients with a clinical suspicion of Glut1DS explored through the reference strategy, i.e., LP and analyses of the SLC2A1 gene; a retrospective cohort that included patients previously diagnosed with Glut1DS. All patients were blind-tested with METAglut1™. In case of discordant results, we performed a functional glucose uptake assay with the patient red blood cells.

Results: We analyzed 428 patients in the prospective cohort, including 15 patients newly diagnosed with Glut1DS, and 67 patients in the retrospective cohort. METAglut1™ was 80% sensitive and >99% specific for the diagnosis of Glut1DS. Concordance analyses showed a substantial agreement between METAglut1™ and glycorrhachia, with a Cohen’s kappa coefficient of 0.78. In the prospective cohort, the positive predictive value of METAglut1™ was slightly higher than that of glycorrhachia. METAglut1™ succeeded to identify Glut1DS patients with SCL2A1 mosaicism and variants of previously unknown significance.

Conclusion: METAglut1™ is an easily performed, robust and non-invasive diagnostic test for the diagnosis of Glut1DS, which allows a wide screening of children and adults with atypical forms of this treatable condition.
Extended duration safety and efficacy of adjunctive ganaxolone treatment in patients with CDKL5 deficiency disorder: 8-month minimum open-label extension follow-up

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Purpose: To report an 8-month minimum follow-up analysis of the open-label extension (OLE) study of ganaxolone in the treatment of Cyclin-dependent kinase-like 5 deficiency disorder (CDD), a developmental epileptic encephalopathy with highly drug-resistant seizures. In a recent placebo-controlled Phase 3 study, ganaxolone significantly reduced major motor seizure frequency (MMSF) in patients with CDD over the 17-week treatment period (ganaxolone 30.7% vs. placebo 6.9%; p=0.0036).

Methods: Patients with CDD (2-19 years of age) who completed the 17-week double-blind phase were eligible to enroll in the OLE. Reductions in MMSF (bilateral motor, >3 seconds) from pre-randomization baseline to 2-month intervals in the OLE, safety, and tolerability were assessed (data cut-off was 24Feb2021).

Results: Eighty-eight of the 101 patients (87.1%) entering the double-blind phase continued into the OLE (43 initially randomized to ganaxolone (GNX-GNX) and 45 to placebo (PBO-GNX). At the time of entry into the double-blind study, median age was 5 years; 79.5% were female, and median monthly MMSF was 50.6. Median treatment time in the OLE was 262 days. In this analysis, 31 (35.2%) patients withdrew from the OLE, with lack of efficacy (38.7%; n=12) and/or adverse events (29.0%; n=9) being the most common reasons for discontinuation. Median MMSF reduction from baseline in the OLE was 30.1% in the GNX-GNX arm (n=38) and 33.3% in the PBO-GNX arm (n=34) at 8 months, and 46.5 (n=22) and 53.8 (n=26) at 12 months. Ganaxolone was generally well-tolerated. No new safety findings emerged.

Conclusions: Safety findings from this OLE analysis are consistent with those from the double-blind phase, as well as the known safety profile of ganaxolone. Data from the OLE provides supportive evidence for maintenance of effect in reducing MMS associated with CDD at approximately 8 months and up to 12 months.

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Longitudinal relationship between seizure burden and developmental progression and the implications on quality of life in children with CDKL5 deficiency disorder

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Purpose: Little is known about what factors may influence the developmental milestones and quality of life (QOL) in children with CDKL5 Deficiency Disorder (CDD). Here we evaluate the effect of seizure and medication burden on developmental progression, and the impact of changes in developmental milestones on QOL in patients with CDD.

Methods: The effects of seizure and medication burden at baseline (high or low) on the CDKL5 Disorder Severity Scores and CDKL5 Developmental Score (CDS) at follow-up were assessed using linear and negative binomial regressions, respectively, with adjustment for age at baseline, gender, and follow-up duration with and without genotype. Seizure and medication burden were defined by average daily seizure count (high, ≥5/day; low, <5/day) and number of antiseizure medications (high, ≥3/day; low, <3/day), respectively. The effects of change in CDS over time (improved, stable, or deteriorated) on Quality of Life Inventory–Disability (QI-Disability) total and domain scores at follow-up were assessed in those aged at least 3 years at follow-up using linear regression models with adjustment for baseline CDS, gender, and follow-up duration.

Results: Almost a quarter (24.8%) of individuals had an improved CDS, and 32.0% had a deteriorated CDS. The average follow-up developmental score was lower for individuals with high baseline seizure burden versus those with low baseline seizure burden [-0.49 (95% CI: -0.84, -0.13)]. Total QOL scores were 5.6 (95% CI: -0.2, 11.5) points higher among those with improved versus stable or deteriorating CDS, and 8.5 (95% CI: 3.1, 13.8) points lower for those with deteriorating versus stable or improved CDS.

Conclusions: Reduced seizure burden in patients with CDD may lead to improved developmental outcomes and better QOL when adjusting for key covariates. Clinical progression for these children may not necessarily be predetermined. It may be positively influenced by optimal seizure management and developmental support.

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Effect of ganaxolone on quality of life in children with the CDKL5 deficiency disorder

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**Purpose:** This analysis explored whether ganaxolone, an investigational drug that has been associated with significant reductions in the frequency of major motor seizures (MMS) in children with CDKL5 deficiency disorder, is also associated with improvements in quality of life (QOL) in CDD.

**Methods:** In a randomized, placebo-controlled trial, 101 children (2-19 years of age; median (IQR) age 6 (3-10) years; 79.2% female; 50 received ganaxolone) with genetically confirmed CDD and ≥16 MMS/month were recruited from 39 sites in 8 countries. Ganaxolone or placebo were administered TID over a 17-week double-blind period. QOL was measured with the Quality of Life Inventory-Disability (QI-Disability) scale. QI-Disability comprises six domains: Social Interaction, Positive Emotions, Negative Emotions, Physical Health, Leisure and the Outdoors, and Independence. The effect of ganaxolone on QOL scores was compared using ANOVA adjusting for age, sex, other anti-seizure medications (ASMs), baseline 28-day frequency of MMS, baseline developmental skills, and QOL scores. ANOVA was also used to evaluate the effect of the percentage change in MMS frequency on QOL scores, adjusting for child age, sex, other ASMs, and baseline QOL scores.

**Results:** After 17 weeks of treatment, total change in QOL score in the ganaxolone group was 4.4 points (95% CI -0.34, 9.07, p=0.068) higher (improvement) than in the placebo group. Changes in Social Interaction domain scores were higher (improvement) in ganaxolone-treated patients (mean difference 7.8, 95% CI -0.30, 15.9, p=0.059), although CIs were wide. Changes in QOL were similar between the two groups for the other domains. Changes in total and domain QOL scores were independent of the co-occurring percentage change in MMS frequency (total QOL score, p=0.705).

**Conclusions:** Accompanying a reduction in frequency of MMS, the ganaxolone group had higher QOL scores than the placebo group when controlling for potential confounding factors, although the estimates lacked precision.

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Aggregated safety and tolerability experience from the Ganaxolone Development Program

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**Purpose:** Ganaxolone is a new chemical entity under investigation for use as an antiseizure medication in rare pediatric epilepsies and status epilepticus. Ganaxolone has been administered to healthy volunteers and subjects with a range of disorders in 46 company-sponsored, Phase 1-3 trials. This analysis summarizes adverse events (AEs) from development programs for ganaxolone in epilepsy and other neuropsychiatric disorders.

**Methods:** Over 1900 study subjects have received at least one dose of ganaxolone. Here we report on the safety and tolerability of ganaxolone in placebo-controlled studies as assessed by the incidence of treatment-emergent adverse events (TEAEs), monitoring of vital signs, physical examinations, electrocardiograms (ECGs), and laboratory tests. Adverse events were coded according to the Medical Dictionary for Regulatory Activities.

**Results:** In placebo-controlled studies, there were 1844 subjects who received either placebo (n=743) or ganaxolone (n=1101). The frequency of TEAEs was 62.9% (693/1101 subjects) for ganaxolone and 53.8% (400/743 subjects) for placebo. The serious adverse event (SAE) rate was similar between ganaxolone and placebo-treated subjects: 2.8% (31/1101) and 3.8% (28/743), respectively. The only serious adverse event reported in more than 2 subjects in the ganaxolone group was seizure (0.5% ganaxolone and 0.7% placebo). The most frequently reported TEAEs (>5% of subjects) and higher in ganaxolone-treated subjects compared to placebo were somnolence (22.4% ganaxolone and 8.1% placebo), dizziness (12.6% ganaxolone and 3.9% placebo), and fatigue (9.3% ganaxolone and 4.8% placebo). CNS-related events appeared to be dose related. There was no discernable safety signal related to bone marrow suppression, bone mineralization, nephrolithiasis, cardiac valvulopathy, or liver function. There have been no significant changes noted in body weight and no clinically significant trends in ECG parameters or vital signs.

**Conclusions:** The experience with the investigational use of ganaxolone in studies conducted to date suggests an acceptable tolerability and safety profile.

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Ganaxolone significantly reduces major motor seizures associated with Cdkl5 deficiency disorder: a randomized, double-blind, placebo-controlled Phase 3 study

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Purpose: To evaluate the efficacy of ganaxolone compared to placebo as adjunctive treatment of major motor seizures (MMS) in CDKL5 deficiency disorder (CDD), a rare, genetically determined developmental and epileptic encephalopathy characterized by early-onset refractory seizures and severe neurodevelopmental impairment. CDD-associated seizures are often refractory to treatment with existing antiseizure medications (ASMs) and improvements may be short-lived.

Methods: In this global, double-blind, placebo-controlled, phase 3 trial, patients aged 2-21 years with a pathogenic CDKL5 variant and uncontrolled major motor seizures (MMS ≥16/month) were randomized to adjunctive ganaxolone (maximum 63 mg/kg/day or 1,800 mg/day, TID) or placebo for 17 weeks. MMS were defined as bilateral tonic, generalized tonic-clonic, atonic/drop, bilateral clonic or focal to bilateral tonic-clonic. The primary endpoint was percentage change from baseline in major motor seizure frequency (MMSF) during the double-blind phase. Key secondary endpoints included ≥50% responder rate and clinical global impression of improvement (CGI-I).

Results: A total of 101 patients (79% female) were randomized, 50 to ganaxolone and 51 to placebo. Patients were a median age of 6 years and had tried a median of 7 prior ASMs. Baseline median 28-day MMSF was 54.0 in the ganaxolone group and 49.2 in the placebo group. Patients taking ganaxolone experienced a median 30.7% reduction in MMSF relative to baseline compared to a 6.9% reduction in the placebo group during the treatment period (p=0.0036, Wilcoxon Rank-Sum Test). Ganaxolone showed numerical trends (not statistically significant) in key secondary endpoints. In subgroup analyses, ganaxolone showed MMSF reductions across the broad CDD population studied. Adverse events occurring in >10% of patients and more frequently in the ganaxolone group were somnolence, pyrexia, and upper respiratory tract infections.

Conclusion: These data provide strong evidence that ganaxolone is effective and generally well-tolerated in the treatment of refractory epilepsy in patients with CDD.

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Ictal asystole with left temporal lobe epilepsy managed by cardiac pacing & resolved following temporal lobectomy: a rare case report

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Purpose: 7 yrs old left handed, Saudi girl with Focal-Lesional left Temporal Lobe Epilepsy, admitted to our EMU at KFSHRC for pre-surgical evaluation, as she had failed 2 Anti Seizure Drugs (ASD). Seizure onset was at the age of 2 yrs, with only 1 consistent semiology.

Method: EMU evaluation: Seizure semiology: Focal unaware: peri oral cyanosis, loss of consciousness, atonia < 5 min. With medication, seizures were reduced to once/ month.

EEG: Focal seizure - left temporal F7,T3 onset. The inter-ictal epochs recorded Generalized 3Hz spike and wave and Occipital Intermittent Rhythmic Delta activity (OIRDA), suggestive of focal epilepsy in addition to a Generalized Epilepsy Syndrome. Asystole recorded for >10 sec, she was symptomatic with perioral cyanosis, Atonia, & altered awareness. No CPR required, Heart Rate picked up after 10-12 seconds.

Cardiology was consulted, & workup with EKG, Echo, Holter was normal but for the ictal asystole a cardiac pacemaker was inserted, and she was continued on 2 ASD and followed in clinic. F/U MRI scans of the lesion cannot be done as it was incompatible with the pacemaker. Neuropsychology at 9 yrs showed sparing of some verbal memory, visual memory was poor, suggesting a transfer of skill, predicting little memory loss after resection. Continued to have infrequent seizures at 9 yrs. At 10 yrs, she had left Anterior Temporal Lobectomy + Amygdalohipocampectomy + dissection

Results: Seizure free post-lesionectomy for 14 months now, with no impact on memory/parents.

Conclusion: We report a rare case of Focal - Lesional left Temporal Lobe Epilepsy, with ictal asystole managed by cardiac pacing, unfortunately with seizure recurrence lesionectomy was done, which made her seizure free. This implies the importance of cardiac pacing for ictal asystole as it is a high risk for SUDEP. Finally tumor resection is important for seizure freedom.
Kabuki syndrome and epilepsy

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Целью данного исследования было изучение распространенности эпилепсии и характеристика синдрома у пациента с синдромом Кабуки (СК).

Было три пациента с СК. Анализировали данные анамнеза, ЭЭГ и МРТ.

Результаты. В результате секвенирования генома все трое необходимы гетерозиготные патогенные мутации в гене KMT2D на хромосоме 12q13. Отмечены фенотипические признаки СК (удлиненная глазная щель, эктропион, сводчатые и широкие брови, широкая переносица, скелетные аномалии, фетальные пальцы, задержка психического развития). У одного из пациентов была диагностирована эпилепсия. У пациента М., посетившего в то время было 20 месяцев, каждый день случался один припадок. Перинатальный анамнез не отягощен, хотя и имеет выраженную задержку развития с рождением. Серийные стали эпилептические припады возникали по 2-3 раза в сутки через 1,5 мес. ЭЭГ использовалась для выявления необычно измененной гипсаритмии. МРТ выявления атрофических изменений в лобных и височных долях головного мозга. В качестве диагноза был идентифицирован атипичный синдром Веста. Терапия вигабатрином, леветирацетамом, вальпроевой кислотой не достигла контроля судорог. Проведен краткий курс гормонотерапии с эффектом связи через 7-8 месяцев, курс был употреблен в комплексе с комплексом свойств. Панель генов эпилепсии оказалась отрицательной. В результате секвенирования генома выявлена мутация гена KMT2D на хромосоме 12.

Заключение. Таким образом, СК имел ранний риск развития эпилепсии на уровне 33%. При начале приступов, хороший ответ на гормональную терапию и неэффективность вигабатрина и других

Epilepsy in temtamy syndrome

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Purpose: Temtamy syndrome is a Genetic disorder with a mutation C1orf57 characterized by variable phenotypic expressivity with visual, cardiac-vascular, Brain malformations. Phenotypic variations are seen at presentation to Neurology services, with No seizures (Sz) while others have intractable Epilepsy on polytherapy Anti-seizure drugs (ASD), Developmental delay, Intellectual disability & speech delay. We aim to study and understand the Genotype and the variable phenotype of Epilepsy in this syndrome, to identify any predictors of risk factors or contributors to the Epilepsy.

Method: This is an Institutional Review Board approved, Multicenter, Retrospective Observational Research study of 20 patients aged 0-14 yrs. All subjects had a + Mutation C1orf57 gene on Epilepsy Genetic panel at King Faisal Specialist Hospital & Research Centre in Riyadh, collaboration with other Tertiary Care centers, 2008 to 2018. Genotype classified into three groups: Homozygous (Founder Mutation), (Novel Mutation), (Novel Mutation)Frame Shift Mutation

Results: Our Cohort showed 65% had Epilepsy, all had sz onset in infancy. 70% had homozygous (Founder Mutation), 23 % (Novel Mutation), 7. 6 % (Novel Mutation) Frame Shift Mutation. Febrile sz (3/9, 33%) were seen exclusively in the Founder mutation group, with intractable Epilepsy + VNS installed (n=1).

Semiology: Generalized Tonic clonic (100%), Generalized Tonic (50%) Myoclonic 40% and Focal sz 10%. Seizure Control: Well controlled sz 53% on Monotherapy. Intractable Epilepsy: 47% on Polytherapy EEG; Abnormal EEG in 50%. No Specific EEG pattern was seen in this syndrome, 50 % of the studies (5/10 EEG’s) recorded: Generalized Spike & wave, slow Background & Multifocal spikes. MRI abnormalities:69%with corpus callosum malformation.

Conclusion: Temtamy syndrome shows a spectrum of Epilepsy, 47% having intractable Epilepsy. The Possible Risk factors &/or Predictors of Intractable Epilepsy in our cohort were found to be the presence of a C.1A>G, P. Met1 Homozygous (Founder mutation) with Febrile sz &/or Abnormal MRI brain (85%).
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Phase 2, placebo-controlled clinical study of oral ganaxolone in PCDH19-clustering epilepsy

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Purpose: This Phase 2 study (Violet Study) assessed the efficacy and safety of ganaxolone in PCDH19-clustering epilepsy.

Methods: This was a randomized, double-blind, placebo-controlled trial conducted at 20 sites in 7 countries. Eligible patients were female (1-17 years of age) with a pathogenic PCDH19 variant and uncontrolled (≥12) seizures (countable focal or generalized seizures with a clear motor component) during a 12-week period prior to screening. Patients prospectively tracked seizure frequency during a 12-week baseline prior to randomization (1:1) to ganaxolone or placebo, which was added to standard of care for the 17-week treatment period. Ganaxolone was taken TID at a maintenance dose of up to 63 mg/kg/day or 1800 mg/day maximum. The primary endpoint was the percentage change in seizure frequency from baseline during the treatment period. Additional secondary endpoints included ≥50% responder rate and clinical global impression of improvement (CGI-I).

Results: Twenty-one patients were randomized (median age of 7.0 years). Patients in the GNX (n=10) and placebo (n=11) groups experienced a median 28-day baseline seizure frequency of 14.5 and 17.7, respectively. Following the treatment period, patients on ganaxolone had a median 61.5% reduction in PCDH19-associated seizures versus 24.0% on placebo (p=0.17). Patients achieving ≥50% seizure frequency reduction were 50% in the ganaxolone group versus 36% for placebo. Clinicians rated 78% (n=9) of ganaxolone-treated patients as “minimally improved” or “better” versus 36% placebo patients. Treatment emergent adverse events (TEAEs) occurred in 70% of ganaxolone and 100% of placebo patients with somnolence being the most common (40% GNX; 27% placebo). One patient on ganaxolone discontinued due to a serious TEAE (psychogenic nonepileptic seizure), which was adjudicated as treatment-related.

Conclusions: Despite the limited sample size, ganaxolone-treated patients experienced directional improvements in seizure frequency compared to those on placebo. Ganaxolone was generally well-tolerated with no new safety findings.

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Epilepsy in children with neurocutaneous disorders – a tertiary center experience

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Purpose: To evaluate the prevalence, features and outcome of epilepsy in children with neurocutaneous disorders (ND).

Methods: The study included children treated in period from 2017 to 2022, with neurofibromatosis (NF), tuberous sclerosis complex (TSC), Syndrome Ito (SI), Sturge-Weber (SWS), Cutis marmorata telangiectatica congenita (CMTC). Epilepsy was diagnosed according to 2014 ILAE definition. Diagnostic criteria for TSC (2012) and NF (Revised 2019) were used. The outcome of epilepsy was assessed at the end of follow up as good seizure control (seizure free/sporadic) or resistant epilepsy.

Results: Retrospective study includes 163 patients with ND. Prevalence of epilepsy was in patients with NF 12/109 (11.0%), in TSC 44/44 (100%) in SWS 5/6 (83.3%), in SI 3/3, in CMTC 1/1. Hemimegalencephaly (HME) was associated with SI in two patients and CMTC in one. Epilpsia partialis continua and refractory status epilepticus were frequent in patients with HME. The mean age at seizure onset (months): one in SI and CMTC, 5.1 in SWS, 23.9 in TSC, 52.2 in NF. After initial focal-onset seizures (25) and infantile spasms (19), children with TSC were suffering focal epilepsy (23), Sy West (15), Lennox Gastaut syndrome (3) and SWAS (1). The outcome of epilepsy was favorable in all patients with NF, 65.9% with TSC, 4/5 with SWS, 1/3 with SI, and in all operated patients (Engel Class 1A)-tuber resection in two TSC and functional hemispherotomy in two HME. One infant with SI and HME died due to super-refractory status epilepticus complicated with ARDS.

Conclusion: The prevalence of epilepsy in children depends of the type of ND and is highest in TSC and SI followed by SWS. TSC is associated with epileptic encephalopathies in 43.2%. HME within NDs is associated with poor outcome, so early surgery has to be considered.
Ictal asystolia in a child with ADNP syndrome: a case report

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Introduction: Helsmoortel-van der Aa syndrome (or ADNP-syndrome) is a rare neurodevelopmental disease caused by de novo mutations in the activity-dependent neuroprotective protein (ADNP). Typical clinical manifestations include developmental delay, autism spectrum disorder, hypotonia, seizures and congenital heart disease. Given the rarity of this syndrome, the type of seizures has not been clearly outlined.

Method: We present a 20 months old male patient, diagnosed with ADNP-syndrome who developed life-threatening seizures associated with severe ictal cardiac bradycardia.

Case: The patient was diagnosed with ADNP-syndrome after birth and developed seizures at the age of 14 months. Seizure semiology began with abnormal breathing sounds followed by apnea, generalized hypertonia and facial cyanosis. Cardiorespiratory and electroencephalographic monitoring during such episodes documented severe desaturation during apnea and motor tonic phase that was followed by extreme bradycardia and eventually asystolia. The bradycardia was attributed to autonomic alterations rather than a consequence of hypoxemia. The aforementioned semiology and the urgent need for cardiorespiratory reanimation motivated a pacemaker implant. The recording of a subsequent seizure following implant showed its effective activation upon bradycardia < 60/minutes and seizure cessation.

Conclusion: To our knowledge, this is the first report of seizures with extreme ictal bradycardia/asystolia in a child with ADNP syndrome. This form of epilepsy is associated with a risk of Sudden Unexpected Death in Epilepsy (SUDEP) and therefore should prompt physicians to consider a pacemaker implant early in care management. The association bradycardia and seizures should be actively searched for in ADNP syndrome.

Epileptic spasms in children: clinical-electroencephalographic aspects

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Introduction: Epileptic spasms (ES) are common in West (WS) syndrome, a devastating encephalopathy up to 2 years. Although rare by definition (occurring in 1 in 3200–3400 live births), ES is a major diagnostic, social and treatment burden in children up to 2 years of age.

Purpose: is to recognize the clinical-electroencephalographic manifestations in ES at early stages, to help the specialists involved in the early detection of the disease.

Material and methods: Retrospective study on a group of 19 children with ES, up to 2 years of age, distributed as follows: 1-3 months (4 cases); 3-6 months (7); 6-12 months (5); > 1 year (3 cases), examined based on anamnesis and video footage. The clinical manifestations and characteristics of the electroencephalographic (EEG) pathways were evaluated and discussed.

Results obtained: The diagnosis of ES was based on the presence of ES (89.5%), their repetitive nature (79%), and preferential on awakening (68.4%). There was an increased incidence in boys (68.4%). At onset: spasm of the eyelids (15.8%) or facial muscles (10.5%); neck muscle strains (21%); trunk tension (21%); limb flexion (15.8%), their extension (10.5%), mixed spasms (5.4%); or isolated (57.9%), symmetrical (26.3%), asymmetric (15.8%). Atypical ES - common in infants (79%). Mental retardation anticipated ES (84.2%), relating to their early onset (89.5%). EEG at onset: burst suppression path (15.8%); typical hypsarhythmia (36.8%), modified hypsarhythmia (31.6%), hypsarhythmia with focal epileptiform changes (10.5%), lack of epileptiform changes (5.3%).

Conclusions: Suspicion of WS at early stages is done by the presence of any type of spasms, associated with a wide variety of electroencephalography and neuropsychic depression. Early recognition of ES and WS etiologies is imperative for the differentiated choice of antiepileptic drug and the prevention of psychomotor disability.

Keywords: Epileptic spasms, West syndrome, electroencephalography.
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Parent reported seizure provoking factors and strategies employed to avoid seizures in children with Dravet syndrome

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Purpose: To describe guardian-reported seizure provoking factors and seizure preventive strategies in children with Dravet syndrome (DS).

Method: In a Swedish population-based study, guardians of 42/47 known individuals with DS born between 2000 and 2018, participated in interviews. Frequency of provoking factors and preventive strategies were compared between children born 2000-2009 and 2010-2018 and children with severe and less severe epilepsy using a Chi square test.

Results: All children had experienced provoking factors and all guardians reported specific strategies to prevent seizures. Seizures had been provoked by a median of seven (range 2-11) out of 13 possible factors and a median of five (range 1-10) preventive strategies out of a possible 11 were reported.

The most common provoking factors were fever (n=42, 100%), afebrile infections (n=39, 93%) and physical activity (n=35, 83%). Afebrile infections ($\chi^2(1,n=41)=6.05$, p=0.014) and reduced temperature ($\chi^2(1,n=40)=7.42$, p=0.006) were more common provoking factors in younger children. Bright light was a more common provoking factor in children with severe epilepsy ($\chi^2(1, n=39)=6.109$, p=.013).

The most common factors avoided were warm weather (n=35, 83%), physical activity (n=27, 64%), and infections (n=25, 60%). It was more common to avoid strong emotions ($\chi^2(1, n=41)=4.4$, p=.035), and reduced temperature ($\chi^2(1,n=40)=5.105$, p=.024) in younger children, and to avoid infections ($\chi^2(1,n=40)=5.105$, p=.024) and crowds ($\chi^2(1, n=38)=3.979$, p=.046) in children with severe epilepsy.

Other prevention strategies included: personal cooling devices (n=22, 52%), seizure alarms (n=20, 48%), home pulse oximetry (n=13, 31%), home oxygen (n=8, 19%) and alternative medicine (n=5, 12%). Many children (n=28, 67%) or their siblings (n=16/34 individuals with siblings, 47%) had stayed at home for fear of infection in school/day-care.

Conclusion: Guardian-reported seizure provoking factors are very common in DS. Guardians employ range of strategies to avoid seizures, placing significant restrictions on family life.

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Lennox Gastaut syndrome diagnosis: changing trends over time - a strategic shift?

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Purpose: Current attitudes to Lennox Gastaut Syndrome (LGS) have suggested favouring less strict diagnostic criteria than the classical triad of intellectual impairment/delay, multiple seizure types and EEG features of slow-spike waves (SSW), with or without paroxysmal fast activity (PFA) in sleep (Arzimanoglou et al. Lancet Neurol. 2009; 8:82-93.1). This audit looks at the evolving patterns of diagnosis over two time periods.

Method: Electronic patient records were reviewed for patients diagnosed with LGS between 2014-2017 and 2018-2021. Patient demographics, clinical features, EEGs, aetiology and medications were analysed. Results were compared against The ILAE diagnostic manual diagnosis (EpilepsyDiagnosis.org. LGS. 2020).

Results: 5 LGS diagnoses were made between 2014-17, compared to 40 diagnoses between 2018-21. All patients in the 2014-17 group had intellectual impairment/delay, multiple seizure types, interictal SSW and PFA in sleep compared to 68% in the 2018-21 group. This increased to 85% when PFA in sleep was excluded from the criteria (2018-21). SSW were present in 100% in 2014-17 vs 90% in 2018-21. Most patients had intellectual impairment when diagnosed and the seizure types were similar in both groups.A male preponderance was noted. Imaging and genetic abnormalities were similar in both groups. The 2014-17 group had a larger proportion of patients with a history of infantile spasms (80%) and autism (80%) compared to the 2018-21 group (23% and 25% respectively). Cannabidiol use (prescribed only after 2018) has increased over time.

Conclusion: There has been a steep increase in the number of LGS diagnoses in the last 4 years, coinciding with UK cannabidiol licencing in 2018. The earlier cohort fits a more classical diagnostic criteria for LGS (including both SSW and PFA in sleep). The 2018-21 group were diagnosed with LGS using less strict criteria, which may reflect the current changing attitudes to the diagnosis, possibly to facilitate access to Cannabidiol.
Scalp HFO rates are higher for larger lesions

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Objective: High frequency oscillations (HFO) in scalp EEG are a new and promising non-invasive epilepsy biomarker, providing added prognostic value particularly in pediatric focal lesional epilepsy. However, it is unclear if lesion characteristics, such as lesion type, localization, and volume impact HFO rates in scalp EEG recordings.

Methods: We analyzed scalp EEG from 13 children and adolescents with focal lesional epilepsy associated with focal cortical dysplasia (FCD), glioneuronal tumors or hippocampal sclerosis. We applied a previously validated automated HFO detector to determine HFO rates in bipolar channels. We identified the type, localization, and volume of the epileptogenic lesion in the MRI.

Results: Both HFO rates (p=0.01) and the number of channels involved in the HFO area (p=0.05) were higher for larger than for smaller lesions. In contrast, HFO rates were independent of lesion type (FCD vs. tumor) or lesion localization (temporal vs. extratemporal).

Conclusions: Our observations support that larger lesions produce higher HFO rates that are encountered over a more extensive area and are thus more accessible to detection than in smaller lesions. Our study provides further insight into scalp HFO variability across patients that may facilitate their implementation as an EEG biomarker in pediatric epilepsy.

Evaluation of the delay in the recognition and treatment of infantile spasms

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Purpose: Infantile spasms are characterized by epileptic spasms with onset in early childhood, usually associated with an electroencephalographic pattern of hypsarrhythmia and abnormal neuropsychomotor development. Infantile spasms are considered a neurological emergency, so early diagnosis is essential, as even a brief delay - as little as 1 week - has been associated with poor long-term neurodevelopmental outcomes. This descriptive study shows the experience of diagnosis and treatment of infantile spasms in an academic infantile neurological service in Brazil.

Methods: We reviewed medical records of 28 children with a diagnosis of infantile spasms or West syndrome seen at a pediatric epilepsy outpatient clinic attended between December 2019 and May 2021. Data regarding medical and sociodemographic factors were collected and described as median and ranges.

Results: The age of children at the onset of spasms varied from less than one month to 10 months (median: 6 months). The time from the onset of spasms to the consultation with a neurologist ranged from 1 to 720 days (median: 45 days), and the median time to the start of treatment was 90 days. The electroencephalogram was performed in 24 children in a median time of 6.2 months after the onset of spasms (range: 3 to 780 days) and all had abnormal results, in which most of them (n=15, 75%) presented hypsarrhythmia. The neurologist's clinical evaluation showed a high prevalence (96.4%) of delay in neuropsychomotor development. Only one child was evaluated with regression. The undefined etiology was observed in most cases (n=13, 46.4%), followed by genetic alteration (n=7, 25.0%); structural alteration (n=7, 25.0%) and congenital infections (n=1, 3.6%).

Conclusion: Our clinical experience suggests a substantial delay in neurologist evaluation and diagnosis of infantile spasms cases, indicating poor knowledge of infantile spasms in primary care settings and contributing to poor long-term neurodevelopmental outcomes.
Predictors of outcome among 31 children with infantile spasms syndrome

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Purpose: Infantile Spasms Syndrome is a severe epileptic encephalopathy. A high number of patients with this seizure type have a neurodevelopmental delay. The main objective of our study was to find out predictors that measure the neurodevelopmental outcome of patients with infantile spasms.

Method: We prospectively evaluated 31 patients with infantile spasms from 2014 to 2017 at three hospitals in Tbilisi, Georgia. Various demographic data were evaluated at the first visit; video-EEG, brain MRI and neurodevelopmental evaluation using ASQ-3™ and Bayley®-III tests were performed upon admission. M-CHAT was performed at the last follow-up in 25 patients. Children were followed for one and two years after the first assessment.

Results: Mean ASQ communication, problem solving and personal-social scores for M_CHAT-N subgroup were significantly higher compared to the risk subgroup. The mean score on the ASQ communication domain was low among structural cases.

Bayley’s mean score for the cognitive domain was significantly higher in children with a favorable neurodevelopmental outcome (74.2) compared to those with developmental delay (58.0) (Mann-Whitney U – 36.5 p=0.007) after two years of follow-up. The same association is observed in the language domain, where we found significantly higher scores among children with normal neurodevelopment (71.5) compared to those with unfavorable outcomes (56.7) Mann-Whitney U – 42.5 p=0.019).

Eleven (92%) out of twelve patients with abnormal neurological examination had a neurodevelopmental delay, while only ten (56%) out of eighteen patients had a delay with normal neurological status at first follow-up (Fisher’s Exact Test - 4.5; df 1; p=0.049).

Conclusion: Our study reveals that abnormal neurological examination, low ASQ and Bayley scores, and structural abnormalities on MRI are predictors of poor development. By using low-cost tests the clinicians should inform parents about prognosis and risk for autism, and start intervention as early as possible to improve development.

Does electrographic overlap between CAE and BECTs indicates unfavorable cognitive prognosis?

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Purpose: The coexistence of generalized epileptiform discharges 3Hz/sec s-w complexes which are hallmark of absence epilepsy (CAE), and epilepsy with centrotemporal spikes (BECTs) in the same or in different EEGs appears to be very rare. The aim of the study was to analyze electrographic features of patients with absence epilepsy who had contemporary or subsequent EEG features of BECTs.

Method: During the 5-year analysis period (2014-2018), 277 children with BECTs and 93 cases with CAE, have been diagnosed and treated at Pediatric Neurology Department, SQUH, Muscat, Oman. In nine of them overlapping of EEG findings seen in these two childhood epilepsy syndrome were revealed and our further research was focused on that group.

Results: The clinical onset of all our patients aged 5-14 years was characterized by absence seizures, either typical (7 children) or atypical (2 children) and in five of them staring was associated with lip smacking. Six out of nine patients presented concomitant electrographic features of both syndromes, whereas 3 patients experienced the EEG pattern of two syndromes at different times, in 2 cases 1 year after, and in one 2 years after absence onset. In all nine patient initial treatment was Valproate, with good seizure control in 6 patient, while in three of them Lamotrigine or Benzodiazepines were added.

In spite of good seizure control 6 patients have poor school performance and in 5 of them comorbidity such as ADHD and learning disability has been found.

Conclusions: Although Childhood absence epilepsy and BECTs have different pathophysiology it is seems that the two phenotypes may connotate neurobiological continuum. A genetic link between idiopathic focal and primarily generalized epilepsies should be consider. In our study group that coexistence of CAE and BECTs can have unfavorable long term prognosis in terms of learning process and school performance.
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Video telemetric epilepsy follow-up augmented by electronic documentation during the corona pandemic

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Introduction: At the Pelzerhaken Children’s center, electronic documentation of seizures and treatment (Epi\Vista®) is used for almost all patients with active epilepsy by the families.

Methods: During the first Corona associated lockdown, we additionally used video telemetric consultations (ClickDoc®) for follow-up. The families have responded well to this form of patient care, which is still used.

Results: We currently perform about 50 video-telemetric follow-up patient contacts augmented by electronic documentation per months. This saves us about 50% of time compared to conventional outpatient clinics, and enables intensified treatment according to patient needs. This technique does not save time in new patients.

Conclusions: Electronically augmented video telemetric care enables intensified and individualized treatment in the home environment of patients. This technique may be helpful in patients with orphan diseases, monogenic epilepsies or drug-resistant epilepsies, who may need intensified and specialized treatment, but may live far away from a specialized centre. Treatment hypotheses might be created and tested during the waiting period for presurgical monitoring. Video telemetric intensified treatment may lead to better adherence.

Literature:

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Unrecognized adverse effects of environmental EMR (electromagnetic radiation) on pre/postnatal neurodevelopment, genetic/reproductive health, and propensity toward early-onset seizures/epilepsy

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Purpose: To review the extensive 70+ year scientific literature assessing the relationship between EMR and epilepsy: increasing EMR exposure of the developing brain may result in increased risk of seizures/epilepsy and related comorbidities, neurodevelopmental disorders, and genetic abnormalities.

Method: Literature review from 1950-2022 using search criteria of EMF, seizure(s), epilepsy, radio-frequency radiation (RFR), EEG, genetic, reproductive, and electromagnetic frequency/radiation.

Results: Exponentially increasing EMR exposure of humans worldwide is essentially unrecognized despite its pervasive, albeit invisible, presence throughout the world. The relationship of seizures/epileptogenesis with EMR exposure from increasingly pervasive wireless networks, cell phones/towers, etc. is demonstrated in numerous publications, also demonstrating adverse effects on genetic/reproductive health. Some neurobiological mechanisms are known, and animal studies are published. The developing nervous system is more susceptible to EMR, and, given that the nervous system functions electromagnetically, neurodevelopmental anomalies and seizures/epilepsy are increasingly associated with such exposures both pre- and postnatally, and throughout the lifespan. Publications also document apparent lack of adverse effects from EMR and warrant further investigation. However, scientists and clinicians should follow the precautionary principle (taking preventative action in the face of uncertain and/or conflicting scientific evidence) given the substantial literature involving human/animal studies and worldwide deployment of wireless technology. Evidence exists that worldwide, pervasive, increasing EMR exposure may result in progressive manifestation of seizures/epilepsy and other disorders of the developing nervous system.

Conclusion: A comprehensive review of adverse effects of EMR confirms that resultant CNS dysfunction may lead to early-onset seizures/epilepsy and associated comorbidities of the developing nervous system, as well as other disorders of pre- and postnatal brain development and genetic/reproductive health. Educational endeavors are needed to raise awareness of the potential harms of daily and cumulative EMR exposure. Simple lifestyle changes are encouraged to diminish daily and cumulative lifetime EMR exposure to the developing child and maturing human.
Ketogenic diet for epilepsy treatment – efficacy and possible predictors. Experience in Children’s Clinical University Hospital, Riga, Latvia

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\textbf{Purpose:} The aim of this observational study was to assess the efficacy of ketogenic diet for epilepsy treatment in Children’s Clinical University Hospital, Riga, Latvia.

\textbf{Method:} The data about paediatric epilepsy patients, that had started ketogenic diet prior to 1\textsuperscript{st} September, 2021, were collected retrospectively from medical records and patient diaries. There were 58 patients, including 30 boys. Median age was 3.14 (IQR 1.94; 7.66) years. The seizure outcome was assessed after 6 and 12 months. The patients with at least 50\% seizure reduction were called responders, but patients with at least 90\% seizure reduction – best responders. Statistical analysis was performed using R (version 4.1.2) and RStudio software. The correlations were estimated with Spearman test.

\textbf{Results:} The diet is still continued by 16 patients, the median duration of the diet for them is 27.3 (18.9; 41.4) months. The median diet duration for the rest patients has been 5.7 (3.0; 13.7) months. The diet was used for at least 6 months in 36 patients. There were 20/58 (34\%) responders, including 8/58 (14\%) best responders. The diet was used for at least 12 months in 26 patients. At this timepoint, 10/58 (17\%) were responders, including 6/58 (10\%) best responders. There was a slightly significant correlation between average first month ketone levels and the seizure reduction after 6-month period (rho = 0.52, p-value = 0.049, data available for 15 patients). Age and sex did not correlate significantly with seizure outcome.

\textbf{Conclusion:} There has been quite good proportion of patients with at least 90\% seizure reduction. Nevertheless, the number of patients with at least 50\% seizure reduction is not so satisfying. It must be noted that the results might be affected by missing data. The average ketone level during the first month might help predicting the diet efficacy during the 6\textsuperscript{th} month.

The landscape of childhood epilepsies: a multi-ethnic population-based study

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\textbf{Purpose:} This study aims to highlight the clinical and epidemiological features of pediatric epilepsy in a cohort of patients from a wide variety of ethnic backgrounds.

\textbf{Methods:} This retrospective cross-sectional analysis reviewed the charts of all pediatric epilepsy patients who were followed between November 2016 and October 2019 at the only tertiary pediatric hospital in Qatar.

\textbf{Results:} The study included 1422 patients of multiple ethnic backgrounds from 55 different countries of origin. 55\% were males. The age of onset was in the neonatal period in 9\% of patients. In the non-neonatal cohort, the average age of onset was 4yrs 9mos (± 1.4mos). Focal epilepsy was the predominant epilepsy type seen in 45\% of patients, versus generalized epilepsy in 37\%. Etiology was unknown in (57\%) whereas structural and genetics causes represented 23\% and 11\% of cases, respectively. Children with genetic and structural epilepsies had an earlier onset of their epilepsy in infancy compared to those with unknown etiologies (%2 years of age). At the last clinic visit, only 36\% of patients were seizure-free. Medically refractory epilepsy was found in 37\% of patients, with the most common etiologies being unknown (36\%) and structural (37\%) in this subgroup. Co-morbidities were present in most patients (62\%), with global developmental delay (47\%) and learning/school difficulties (22\%) being the most prevalent. Factors associated with an increased risk of co-morbidities and/or medically intractable seizures were early age of onset (<2 years of age); presence of antenatal risk factors; history of previous central nervous system infection; history of status epilepticus and a family history of consanguinity and epilepsy.

\textbf{Conclusion:} This multi-ethnic population-based study confirms the findings of epidemiologic studies done elsewhere. In addition, it highlights risk factors for developing co-morbidities and medically-intractable seizures in children with epilepsy.
Expanding the phenotypic and neuroimaging spectrum of PLPBP-related pyridoxine-dependent epilepsy

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Background: A relatively new subgroup of pyridoxal phosphate binding protein (PLPBP) has recently been identified as a cause of pyridoxine-dependent epilepsy.

Purpose: To further delineate the phenotype of PLPBP variants.

Method: Retrospective review. We present clinical, molecular, and radiographic data from 8 unrelated cases with PLPBP variants and compare their presentation to previously reported cases.

Results: Perinatal history was remarkable for: fetal distress in 2 patients, and microcephaly in 3 patients. All affected infants had seizures between day 1 and day 3 of life. Myoclonic seizures were the most frequent seizure symptomatology (4/8). Burst suppression (3/8) and multifocal spike discharges (3/8) were the commonest interictal EEG findings. The most frequently reported biochemical abnormalities in patients with PLPBP mutation which were evident in our study: metabolic acidosis with hyperlactatemia (3/8), anemia (3/8), and hyperglycinemia (1/8). MRI brain revealed global brain atrophy in all subjects (8/8), periventricular germinolytic cysts in (3/8), and other brain malformations (lissencephaly in 1 patient, and focal cortical dysplasia in 1 patient). Pyridoxine therapy resulted in an immediate reduction in seizure frequency and severity in all patients; none experienced respiratory depression. All patients were left with acquired microcephaly, variable degree of developmental delay (severe in 6/8, mild to moderate in 2/8), and 7 patients required additional anti-seizure medications.

Conclusion: This study expands the clinical, laboratory, and neuroimaging spectrum of PLPBP-related disease.

Severe epileptic encephalopathy in patients with Down syndrome caused by double genetic pathology

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Purpose: The incidence of epilepsy in patients with Down syndrome (DS) is higher than in the general population, while severity of the disability may vary between individuals (Verrotti A et al. J Pediatr 2013; 163:1754-1758). We present three patients with DS and epileptic encephalopathy, in which further diagnostic evaluation including genetic analysis revealed a concomitant genetic disease.

Method: Case series.

Results: The first patient is a 15-year old girl with DS who presented with epileptic spasms, myoclonic and focal seizures at the age of 5 years. In the following years, her condition deteriorated as she developed severe epileptic encephalopathy, psychiatric symptoms, and severe developmental delay. Due to severity of her clinical picture, we performed additional genetic analysis which revealed a mutation in GLDC gene related to nonketotic hyperglycinemia. The second patient is a 14-year old boy with DS who presented with infantile spasms and severe developmental delay during infancy. Cardiological evaluation revealed heart rhabdomyoma, and additional genetic analysis confirmed a mutation in TSC2 gene related to tuberous sclerosis complex. The third patient is a 11-year old boy with DS who started with infantile spasms at the age of 6 months, followed by severe developmental delay and later autism. Infantile spasms were refractory to treatment with VGB, ACTH and other antiepileptic drugs. Additional genetic analysis revealed a mutation in gene KANSL1, which most likely contributed to the severity of phenotype.

Conclusions: All three patients with DS in our cohort had epileptic encephalopathy, which was pharmacoresistant in two patients, and severe developmental delay. The severity of clinical phenotype warranted further genetic analysis which revealed a concomitant genetic disease. Two patients benefited from novel genetic insight, as we modified the treatment which resulted in an improvement of the clinical picture. We recommend further genetic evaluation in difficult to treat patients with DS.
Prognostic factors and seizure outcome in posterior reversible encephalopathy syndrome (PRES) in children with malignancies

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Purpose: The aim of this study was to evaluate seizure outcome in children with hematological malignancies and PRES and to identify prognostic factors that could help manage the syndrome.

Methods: We retrospectively reviewed the report data of 21 patients diagnosed with hematological malignancy or aplastic anemia and PRES between 2008 and 2018. Basic demographic data, oncology treatment, presymptomatic hypertension before PRES manifestation, neurological status, seizure type, and EEG and MRI findings at PRES onset and at the one-year follow-up visit were studied. Patients who developed remote symptomatic seizures or epilepsy were identified.

Results: We included 21 children (11 females and 10 males) in the study. Sixteen patients (76.2%) were diagnosed with ALL and the rest individually with AML, CML, T-lymphoma, Burkitt lymphoma, and severe aplastic anemia. Presymptomatic hypertension (PSH) was evaluated in 19 patients and was present in 18 (94.7%). The duration was 9 h and more in 16 patients (88.8%); the severity was grade II in 12 patients (66.7%). Seizures as the initial symptom of PRES were present in 17 patients (80.9%). Four patients (19.0%) were assessed with remote symptomatic seizures. Two of them (9.5%) had ongoing seizures at the one-year follow-up visit and were diagnosed with epilepsy. The presence of gliosis on follow-up MRI indicated worse outcome with development of epilepsy (without statistical significance).

Conclusions: PRES syndrome has an overall good prognosis and the evolution to epilepsy is rare. The severity and duration of PSH or seizure severity and EEG findings at PRES onset were not associated with worse neurological outcomes in this study.

ARX-related infantile spasms and severe complex movement disorder

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Epilepsy caused by ARX mutation is one of the rare epileptic syndromes associated with movement disorders. X-linked severe dyskinesias like generalized dystonia, choreoathetosis together with infantile spasm and mental retardation in males have been described in literature. However, detailed clinical reports of patients with infantile spasms and dyskinesias carrying ARX mutations are limited.

Here, we present a clinical features of 4 year-old boy with infantile spasms, mental retardation and severe dystonia and choreoathetosis caused by a hemizygous mutation of the ARX gene, as confirmed by exome sequencing. The patient we describe is the second child of healthy non-consanguineous parents. He was first brought to medical attention at 5 months of age because of the onset of clusters of flexor spasms when falling asleep or awake. An electroencephalogram (EEG) was performed which showed modified hypsarrhythmia (fig 1). The choreoathetosis was noticed at 6 months, soon after the first spasms. At that time, the neurological examination showed global psychomotor delay with poor interaction, absent social smile. The severe, debilitating, long-lasting mix of choreoathetosis and dystonia appeared periodically once per 9-12 months lasting about 15-25 days, intermitting with a cluster of spasms. We observed several types of movement disorder in our patient consisted of continuous choreoathetosis of four limbs, tongue protrusion, generalized dystonia, oculogyric crisis and status distonicus lasting few day. He could not achieve head control and sitting.

The WES revealed a hemizygous inframe-insertion variant c.321_341dup, p.(Ala109_Ala115dup) in the ARX gene (NM_139058.3).

In conclusion, our study describes a phenotype in a male associated with a loss of function variant in ARX. This case suggests ARX as a potential cause of the disease in male patients with severe phenotypes-infantile spasms, severe movement disorders and developmental delay.
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Treatment-response and long-term prognosis in patients with electrical status epilepticus in sleep

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Purpose: ESES is defined as continuous epileptiform activity persisting during 50-85% of the NREM-sleep and associated with developmental arrest, slowing or regression and cognitive and behavioral decline. The goal of treatment is to normalize or reduce sleep related EEG epileptiform activity significantly, a change that should lead to improved functional outcome.

We describe the etiology, clinical characteristics, treatment-response and long-term outcomes in patients with ESES.

Methods: We reviewed the medical records of children with ESES at the tertiary pediatric epilepsy clinic in Edmond and Lily SAFRA children's hospital between the years 2005-2019. The collected information includes demographic and clinical data, therapeutic regime (AED's alone or combined with steroids) and outcomes.

Results: The average time of follow-up was 82.25 months. Of the 101 children concluded in the study, 89 (88.1%) of the children had resolution of ESES under treatment. Seventy children (69.3%) were treated with steroids. Almost all of them were treated with combination of IV and oral steroids. Among them, 42 (60%) responded to treatment. Twenty-five of the children that responded to steroids had relapse of ESES. They were further treated with repeat course of steroids or with AED's, and in last follow-up only 7 (10%) had ESES.

The majority (71.3%) of the children had functional improvement at last follow up compared to baseline. Nonetheless, 63.4% attend special education programs or have learning disability. Children who had resolution under steroids treatment had less functional improvement at last follow up (p-value<0.03).

Conclusions: We show high resolution rate for ESES and good functional outcome in long term follow up in a broad patient population. Approximately half of the children responded to steroid courses. Children who were treated with steroids often have more refractory ESES and different underlying pathology than the ones responded to AED's which may partially explain their inferior functional outcome.

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Clinical characteristics of paediatric patients with low-grade gliomas and epilepsy

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Purpose: Low-grade gliomas (LGG) are the most common epilepsy associated paediatric brain tumors. The aim of this study was to evaluate the clinical characteristics of a cohort of paediatric patients who were diagnosed with LGG with focus in epilepsy.

Method: For purpose of this retrospective study, medical records of paediatric patients with LGG in the years 2011-2020 were evaluated. Data on patient age at diagnosis, gender, tumor histology and location, seizure type and therapy were collected from those who had seizures.

Results: 18/82 (22%) LGG patients had seizures, with a mean age 9.8 ± 6 years (range 0-18 years) at the time of diagnosis. In patients with seizures, 66% were male. Ten LGG were of glial-neuronal origin (6 ganglioglioma, 4 dysembryoplastic neuroepithelial tumors) and 8 of astrocytic or oligodendrogial origin (4 presented subependymal giant cell astrocytoma (SEGA) in tuberous sclerosis patients). All tumors were located in the supratentorial area: 9 in the temporal lobe, 4 in the frontal lobe, 1 in the suprasellar region and SEGA around Foramen Monroe. Focal seizures and focal onset seizures with impaired awareness were most frequent seizure types. Levetiracetam, oxcarbazepine, carbamazepine, valproate and lamotrigine were the most common antiepileptic drugs. 14 patients, except SEGA, had surgery: 9 epilepsy surgery and 5 tumor surgery, with residua left in 4 patients due to risky tumor location. One patient with diffuse astrocytoma needed additional chemotherapy. Thirteen out of 14 (93%) operated patients were seizure free at average follow-up 6.2 ± 2.9 years (till the end of 2021).

Conclusion: One fifth of patients with LGG in our cohort developed epilepsy. All LGG were located in the supratentorial region and focal seizures with or without impaired awareness were the most common seizure types. Surgical treatment resulted in seizure freedom in most patients.
Analysis of SNP and CNV polymorphisms and variants in genes related to metabolism and effects of cannabinoids in refractory epilepsy in children - a pilot study

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Introduction: Integrating molecular diagnostics into clinical and research procedures has proven that genetic factors contribute to individual variability in response to antiepileptic drugs. This applies to both seizure control and adverse effects associated with antiepilepsy therapy. This variability results from different mechanisms of pharmacokinetics and pharmacodynamics (for example, polymorphisms in genes encoding enzymes that metabolise drugs or are potential effectors of brain AEDs, such as receptors or ion channels), variants in 'epilepsy-inducing genes' or modifications in the expression of epilepsy or alterations in the expression of enzymes and other molecules involved in pathogenesis of pharmacoresistance or adverse drug reactions.

Methodology and study group: Genetic analysis by next-generation sequencing (NGS) was performed in a group of 28 children diagnosed with drug-resistant epilepsy (West syndrome, Lennox-Gastaut syndrome). In its scope, exome sequencing (ES) analysis was performed in terms of copy number variation (CNV) and single nucleotide polymorphisms (single nucleotide polymorphism, SNP).

On this basis, the probable cause of the disease was determined in 11 subjects (pathogenic or probably pathogenic variants were identified in genes: ABAT, CACNA1H, CHD, DEPDC5/SIK1, KCNQ2, PIGN, SCN1A (2 patients), SCN2A, SIK1, SPTAN1 and SZT2.

The analysis also included 61 polymorphisms in 18 genes, which are known to be involved in the metabolism of antiepileptic drugs and cannabinoids.

Results: The study group showed a significantly different allele frequency (AF) from the population for polymorphisms in genes: CNR1, CYP1A, CYP2C9, CYP3A4, CYP3A5, GABRA1, HNF4A, OPRM1, SCN1A, UGT1A6.

Conclusions: The broad cannabinoid metabolic pathway in the human body, as well as individual genetic variability in the population, may cause variable responses and lead to different effects of cannabinoids. This study will characterise a group of paediatric patients with drug-resistant epilepsy in terms of the presence of genetic variants that may determine the response to cannabinoids.

Levetiracetam vs. phenobarbital for neonatal seizures: evaluation of a paradigm shift

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Purpose: Although phenobarbital (PB) is commonly used as a first-line anti-seizure drug (ASD) for neonatal seizures, in 2015 we chose to replace it with levetiracetam (LEV), a third-generation ASD. In this study, we compared the safety and efficacy of LEV and PB as first-line ASDs, considering the years before and after modifying our treatment protocol for neonatal seizures.

Method: We performed a retrospective study of 108 consecutive neonates with EEG-confirmed seizures treated with first-line LEV or PB in 2012-2020.

Results: First-line ASD was LEV in 33 (31%) and PB in 75 (69%) neonates. The etiology included hypoxic-ischemic encephalopathy (HIE) in 31% of cases, intracranial hemorrhage in 15%, ischemic stroke in 9%, and neonatal-onset genetic epilepsy in 19%. Forty-two of 108 (39%) neonates achieved seizure freedom following first-line therapy. Treatment response did not vary by first-line ASD in the full cohort (LEV, 15/33 = 45%; PB, 27/75 = 36%; p = 0.28) or in the HIE subgroup (LEV, 5/10 = 50%; PB, 9/23 = 39%; p = 0.52). Treatment response was lowest for neonates with a higher seizure burden, particularly for neonates with status epilepticus than those with rare seizures (p<0.001) but did not differ by sex, gestational age, etiology, or EEG background. Adverse events were noted in 22 neonates treated with PB and only in one treated with LEV (p<0.001).

Conclusion: PB was associated with more adverse events than LEV, and the two ASDs were equally but incompletely effective in treating neonatal seizures, thus confirming LEV as a safe and effective alternative to PB as a first-line therapy in these neonates.
Seizure evolution and outcome in pediatric autoimmune encephalitis

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Purpose: Our study aimed to characterize seizure incidence, evolution, and outcome of pediatric autoimmune encephalitis (AE) focusing on subgroup analysis based on type and presence of antibody (Ab) to neuronal antigens.

Method: We compared seizure characteristics and outcomes in 68 patients with seizures among 110 patients, who satisfied the proposed criteria of pediatric AE. The Ab-positive group included patients with anti-MOG and anti-NMDAR antibodies. The Ab-negative group was defined according to recently proposed criteria. Univariate and multivariate analyses were performed to evaluate the risk factors for postencephalitic seizures, defined as persisting seizures six months after onset.

Result: Seizure incidence in the anti-MOG group (37.8%) differed from that in the anti-NMDAR (88.9%) and Ab-negative (71.1%) groups. Median seizure frequency within 6 months was higher in the Ab-negative group (6.0, interquartile range [IQR] 3.0–13.0) than in the anti-NMDAR group (3.0, IQR 2.0–4.5) and anti-MOG group (2.0, IQR 1.0–5.0). Patients in the Ab-negative group tended to develop postencephalitic seizures more frequently and have a lower seizure freedom rate than those in the anti-NMDAR and anti-MOG groups. Ab-negative status, high seizure frequency within 6 months, and the presence of status epilepticus were associated with the development of postencephalitic seizures on univariate analysis. On multivariate analysis, Ab-negative status remained the only significant variable linked with postencephalitic seizure (Odds Ratio, 4.17; 95% Confidence Interval, 1.02–18.05).

Conclusion: We delineated the seizure incidence, evolution, and outcome of Ab-positive and Ab-negative pediatric AE patients. Ab-negative status is predictive of higher seizure burden, more frequent development of postencephalitic seizures and less favorable seizure outcome than anti-NMDAR and anti-MOG Ab-positive status.

The new trend for antiseizure medication selection in juvenile myoclonic epilepsy: a retrospective multi-center study from Turkey between 2010 and 2020

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Purpose: Valproic acid (VPA) is a frequently used and effective drug in treating juvenile myoclonic epilepsy (JME) (1). Recently, levetiracetam (LEV) has been suggested for monotherapy in patients with JME (2). This study aimed to evaluate the antiseizure medication therapy in patients with JME.

Methods: A total of 257 cases (152 girls, 105 boys) with the JME included in the study cohort between 2010 and 2020 were evaluated retrospectively. The seizure remission was defined in patients who were seizure-free for at least 12 months. Results: VPA was preferred in 131 cases (50.9%), LEV in 114 cases (44.4%), and lamotrigine (LTG) in 29 cases (10.7%) as the first choice of antiseizure drug. The first drug choice was VPA in 73.3% male cases and LEV in 57.8% female cases. A statistically significant difference was determined between both genders regarding the first drug choice (p<0.001). In the first five years (2010-2015), VPA (n=66.64%) was preferred the most, and in the last five years, LEV (n=83, 57.1%) was the first choice (p=0.005). The most frequent reason for discontinuation was ineffective for LEV and adverse effects for VPA, which was statistically significant (p=0.001). During follow-up with treatment, 237 cases (92.2%) were seizure-free for at least 12 months, while 159 of them (61.9%) were also in electrographic remission. Seizure remission occurred earlier than EEG remission (p<0.001).

Conclusion: This study clearly reveals that LEV has been preferred more frequently as the first drug in the treatment of JME in recent years. Although LEV is more advantageous due to its low adverse-effect profile, it is still considered that VPA is more effective in terms of seizure control.

References:
Myoclonic status in non-progressive encephalopathies: longitudinal study of 55 patients

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Purpose: Myoclonic Status in Non-Progressive Encephalopathies (MSNPE) is an epileptic encephalopathy characterized by the occurrence of long-lasting atypical status epilepticus associated with a subcontinuous delta-theta monomorphous activity at the EEG, attention impairment and multifocal erratic myoclonia, leading to a cognitive decline (Dalla Bernardina B et al Boll Lega It Epil 1980;29-30:183-7). We report the electroclinical study of 55 patients with MSNPE, longitudinally followed for a median period of 11 years.

Method: Following data were collected for each patient: epilepsy history, neurological and neuroradiological features, age at MSNPE onset and its electroclinical characteristics. For patients with aged over 6 years (n=39), data regarding neurological outcome and course of the MSNPE were also obtained. Basing on electroclinical features, 3 types of MSNPE were outlined (Elia M. et al Epilepsia 2009;50Suppl5:41-4). Type 1: MSNPE with positive myoclonia; Type 2: MSNPE with prominent negative myoclonia and dystonic movements; Type 3: MSNPE associated with progressive deterioration of the electroclinical picture.

Results: Thirty-eight (69%) had a genetic etiology: 24 showed a Type 1 MSNPE (Angelman Syndrome, Wolf-Hirschhorn Syndrome, 5q14.3 deletion, 17q12 duplication); 6 showed a Type 2 MSNPE (CDKL5, ARV1, KCNB1, KCNQ2, 14q12 deletion); 8 showed a Type 3 MSNPE (Angelman Syndrome, SCN8A). Two patients had epilepsy due to pre-perinatal hypoxic-ischemic encephalopathy (Type 1 and 2). In fifteen patients etiology was unknown, 4 showing Type 1 (negative MRI in all), 6 showing Type 2 (positive MRI in 3), and 5 showing Type 3 (positive MRI in 1). Patients with Type 1 showed a better outcome in terms of MSNPE course, neurological features and epilepsy.

Conclusion: This study further contributes to define the MSNPE, which is still underdiagnosed. Considering its unfavorable outcome, MSNPE should be early identified in order to start an appropriate treatment and a close clinical monitoring (Caraballo R et al Seizure 2017;51:1-5).

Myoclonic absence seizures: a single-center long-term longitudinal retrospective study

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Purpose: We aim to describe the electroclinical phenotypes and the longitudinal evolution of patients presenting with myoclonic absence seizures in order to highlight potential grouping variables and prognostic factors.

Method: We retrospective evaluated demographics, clinical data and electroencephalographic findings of 39 patients followed at Child Neuropsychiatry Unit of Verona presenting with myoclonic absence seizures through the course of their epilepsy. We analysed collected variables by means of descriptive statistic, than performed a cluster analysis. Results: The mean age at epilepsy onset of the entire cohort is 28.9±30.6 months, while the onset of myoclonic absence seizures occurred at the mean age of 42.0±37.5 months. About one quarter (10/39) of patients uniquely presented myoclonic absences in the disease course. The mean age at last follow-up was 160.9±89.4 months and 41% (16/39) of patients was seizure free. Cognitive function was preserved in 25%, of the cases, while for the remaining a cognitive impairment of various degrees was detected. Cluster analysis allowed the identification of two subpopulations which differ significantly for: types of seizures presented at onset, types of seizures during the disease course, age at seizure onset, seizure freedom at last follow-up, and aetiology. The cognitive outcome of the two subgroups was significantly different.

Conclusion: In patients with myoclonic absence seizures two subpopulations can be identified with distinctive presenting features and significantly different disease outcomes.
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Syntactic, lexical, and reading difficulties in adolescents with childhood epilepsy with centrotemporal spikes

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Purpose: We investigated several language domains such as syntax, lexical retrieval, phonological short term memory and reading skills in children with Childhood epilepsy with centrotemporal spikes (CECTS) and compared them to typically developing children.

Method: Children with CECTS aged 9 -18 (n=24) were tested to assess the following parameters: syntax using tasks for evaluation of comprehension and production of sentences with syntactic movement and pronouns; lexical retrieval by picture naming, phonological working memory using word span tests and various word reading tests for various types of developmental dyslexia. Correlations were performed between age at diagnosis, location of epileptic focus, spike-wave index in sleep EEG, frequency of seizures, response to antiepileptic medications treatment.

Results: 22/24 children had a language deficit in at least one of the domains tested p<0.01. 15 the children had syntactic movement deficit as they performed better on tasks involving comprehension, production and repetition of subject relatives than on object movement structures. 14 children had difficulties in lexical retrieval and similar number of participants had phonological short-term memory deficit. Deficits in pronouns comprehension and production were found in 8 children. 4 types of dyslexia was found in 14 children compared to 10% in the school age typically developing children.

Conclusion: Our study confirmed previous findings that CECTS co-occur with impaired language and reading abilities. The language-related tasks studied have not been previously used among this specific population (CECTS). The majority of study children had a syntactic deficit, specific to syntactic movement. Reading deficits included surface dyslexia, vowel letter dyslexia, attentional dyslexia and letter position dyslexia. Naming deficits (anomia) resulting from deficits in various components, most commonly in the phonological output lexicon and in the phonological output buffer. Referral of affected children to a tailored speech therapy may have a great effect on their academic performance and social interactions.

Pandemic Response

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Risk of hospitalization and death for COVID-19 in persons with epilepsy: the EpiLink Bologna cohort, Italy

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Purpose: Persons with epilepsy (PWE) show a paradigmatic pattern of vulnerability, due to seizures, antiseizure medications-relate adverse events and, in the subgroup of patients with developmental and/or epileptic encephalopathies (PEE), intellectual disability. Data on COVID-19 outcomes in PWE are scarce. We aimed to study the risk of hospitalization and death for COVID-19 in a cohort of PWE from 01 March 2020 to 30 October 2021.

Method: Historical cohort design (EpiLink Bologna), comparing adult PWE with at least one outpatient visit in 2018 and 2019 at our epilepsy center, grouped in people with focal epilepsy (PFE), idiopathic generalized epilepsy (PIGE) and PEE, and a matched population cohort (ratio 1:10) for age, sex, comorbidity and residence, living in the local health trust of Bologna (about 800000 residents). Clinical data were linked to health administrative data.

Results: In both cohorts (EpiLink N=1576 subjects, 1128 PFE, 267 PIGE, 148 PEE, 32 other; controls N=15326 subjects), 52% were females and mean age was 50 years (SD 18). Hospital admissions for COVID-19 in the whole period were 49 (3.1%) in PWE and 225 (1.5%) in controls. The adjusted hazard ratio (HR) in PWE was 2.0 (95% CI 1.4-2.7). The subgroups at higher risk were PFE (HR 1.9; 95% CI 1.3-2.8) and PEE (HR 3.9; 95% CI 1.7- 8.7), while PIGE had a HR of 1.1, i.e. similar to the control group (95% CI 0.3-3.5). Two-month risk of death was 18% both in PWE and controls.

Conclusion: During the first two epidemic peaks in Bologna, PWE (namely PFE and PEE) had a doubled risk of COVID-19 hospital admission compared to a control population. Conversely, epilepsy did not represent a risk factor for COVID-19-related death.
Impact of COVID-19 on the course of Infantile Spasms syndrome

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Purpose: The aim of the study was to assess the impact of Coronavirus disease-19 (COVID-19) on the course of Infantile spasms syndrome (ISS).

Methods: We conducted this ambispective study at a tertiary-care centre in North India. The study design was approved by Institute Ethics Committee. Inclusion criteria were diagnosis of COVID-19 based on RT-PCR in children diagnosed with ISS.

Results: Between December 2020 and August 2021, of 70 children screened, five children with ISS (four prospective, one retrospective) fulfilled eligibility criteria and participated in the study. Of five children, three were girls, and two were boys. The median age at presentation with COVID-19 was 18.5 months. Three children had underlying acquired structural etiology, one had tuberous sclerosis complex, and one had presumed genetic etiology. At the time of COVID-19 illness, three children were in remission following standard therapy, while two had ongoing epileptic spasms. Of three children with remission, two continued to be in remission while one suffered a relapse. Of two children with persistent spasms, one had no change, and the other had transient clinical cessation of epileptic spasms for three weeks from day 2 of COVID-19 illness. However, electroencephalography, performed on day eight of illness, demonstrated hypsarrhythmia. Pyrexia was the most prominent symptom of COVID-19 (duration ranging from 1-8 days). The severity of COVID-19 was moderate in two children requiring hospitalization, while the three had a mild illness. All five children had a complete recovery from COVID-19.

Conclusion: Our study is a rare case series of COVID-19 in children with ISS. We observed a variable severity of COVID-19 illness and a varying impact on epileptic spasms.

COVID 19 and the global situation of epilepsy care

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Purpose: The COVID-19 pandemic contributed to changes in healthcare delivery across the globe. This study aimed to explore changes in epilepsy care delivery patterns and teleconsultation methods in resource-poor settings during and since the lockdown.

Methods: A cross-sectional online survey was conducted among healthcare professionals (N=240) from 23 countries caring for people with epilepsy (PWE). Epilepsy provider representatives identified from each country distributed the survey. The Chi-square test, \( \alpha=0.05 \), pairwise multiple comparisons conducted via Bonferroni, \( \alpha=0.017 \) were used for data analyses.

Results: Participants were from lower middle-income country (LMIC; n=53), upper-middle income country (UMIC; n=165), high income country (HIC; n=22), and from four regions (Africa 5.6%; Asia 31.2%; Caribbean 12.4%; Latin America 50.8%). Majority of participants were from urban (97.1%) and public health settings (83.2%). The major concern for PWE during the pandemic was difficulty in reaching physicians/healthcare providers (\( P=0.006; \ HIC<LMIC; \ HIC<UMIC \)). There were no significant differences in concerns such as difficulty in getting medication, difficulty reaching and urgent care facility or medication availability in the pharmacy. The major barriers since the pandemic were financial trouble – reduced income/expenses to travel (\( P<0.001; \ UMIC<LMIC; \ UMIC<HIC \)), lockdown (\( P=0.01; \ UMIC<LMIC \)), clinic closure (\( P=0.005; \ UMIC<HIC \)), long waiting times at clinics (\( P=0.009; \ LMIC<UMIC, \ HIC \)). No significant differences were found for barriers such as transportation disruption, fear of getting infected with CoV-2 or healthcare worker shortage. Restricted services were lab work (\( P=0.02 \)), EEG, MRI, and CT. The teleconsultation methods used were SMS (\( P=0.01; \ UMIC<LMIC \)), social media including WhatsApp, WeChat, Facebook messenger, and telephone calls.

Conclusion: Healthcare delivery in resource-poor settings have been as, or more, affected by COVID. Access to services such as EEG and neuroimaging were heavily impacted and rapid conversion to various methods of teleconsultation required. Such disruptive conditions are often disproportionally felt by many LMIC countries.
Is there an association between epilepsy and COVID-19 infection and an increased risk of seizure recurrence?

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Purpose: The problem of the association of COVID-19 with the dynamics of epilepsy seizures has not been thoroughly investigated. The objective of this study was to examine the dynamics of seizures in patients with epilepsy who had had COVID-19, based on clinical observations and analyses of seizure progression.

Method: The study design was a retrospective uncontrolled open-label multicenter observational study of the impact of COVID-19 on the course of epilepsy. Between June and December 2021, patients with epilepsy who had had COVID-19 were interviewed using a questionnaire with three sets of questions.

Results: The study included 30 with epilepsy who had had COVID-19: 12 cases of hereditary (idiopathic) generalized epilepsy (40%) and 18 cases of focal epilepsy (60%). The mean age was 33 years. The male-to-female ratio was 2:3. Before COVID-19, 19 patients (63%) had seizure remission, while 11 patients did not have seizure control (37). AED monotherapy was administered to 57% of patients, polytherapy to 37% and no therapy to 6% of cases. Dynamics of epilepsy: unchanged - 80%, reduction in the frequency of seizures - 7%, worsening course - 13% (4 patients: 2 cases of generalized epilepsy, 2 cases of focal epilepsy. 3 patients who had previously been seizure-free had relapsed. Seizures became more frequent in 1 patient.)

Conclusion: COVID-19 does not exacerbate epilepsy dynamics in the majority of cases, and it has only been associated with a worsening course of epilepsy in 13% of patients.

COVID-19 vaccination in patients with epilepsy: patients opinions on the necessity of COVID-19 vaccination

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Purpose: Due to the high demand for information regarding COVID-19 vaccination in people with epilepsy (PWE), we assessed PWE opinion on the reasons for the necessity of COVID-19 vaccination.

Method: The study design was a two-centre retrospective uncontrolled open-label observational study of the impact of COVID-19 vaccination on the course of epilepsy. Adult patients who were treated at two epileptological centres were asked to report on their vaccination status and, if vaccinated, about their opinion on the reasons for the necessity of COVID-19 vaccination. PWE were interviewed between June and December 2021 using a questionnaire containing three sets of questions. Descriptive statistics were used.

Results: The study included 58 vaccinated PWE. 13 PWE discontinued the study. 45 PWE opinions on the reasons for the necessity of COVID-19 vaccination were collected.

The mean age was 33 years. Male/female ratio = 2:3. Health care was the main reason for vaccination- 20 cases (44.4%), second- job requirement - 11 (24.4%), the third- fear of COVID-19 and/or death - 8 (17.8%), Seldom reasons-social responsibility-2 (4.5%), other (including tourism) - 4 (8.9%)

Conclusion: These data can help policymakers understand the concerns of these patients with epilepsy and the population as a whole.
**Purpose:** To assess the impact of COVID-19 illness and COVID-19 pandemic era with government restrictions, so-called lockdowns, on the course of epilepsy, sleep, health care, and social status in patients with active epilepsy.

**Method:** Our designed and approved questionnaire consisted of 23 questions. We focused on
(1) demography,
(2) course of epilepsy,
(3) subjective assessment of sleep,
(4) health care continuity, and
(5) employment and social status of patients with active epilepsy during the first year of the COVID-19 pandemic in the Czech Republic from March 2020 to May 2021.

The questionnaires were administered during outpatient visits or by phone calls in three major Czech epilepsy centers (Ostrava, Brno, Pilsen).

**Results:** We enrolled 227 patients with active epilepsy into the study. The mean age of our sample was 41.2 ±14.82 years (min 18, max 86 years), and 138 (61%) were women. COVID-19 was diagnosed in 57 (25.1%) patients. The illness had no significant impact either on the frequency and severity of the seizures (p= 0.631, p=0.792 respectively) or on the subjective perception of general health (p=0.345). Sleep-related seizures dispose to sleep impairment (p=0.014) and vivid dreams and nightmares (p=0.033). COVID-19 significantly increases the risk of vivid dreams and nightmares in patients with seizures during wakefulness (p=0.006). The three centers provided adequate outpatient care during the first year of the pandemic. The employment and social status of the patients with epilepsy remained unchanged (p=0.074).

**Conclusion:** COVID-19 infection did not affect the course of epilepsy. COVID-19 significantly increases the occurrence of vivid dreams and nightmares in patients with seizures in wakefulness.

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**Psychiatry**

**79 Functional (psychogenic non-epileptic / dissociative) seizures: why and how?**

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**Purpose:** Functional seizures (FS) known also as psychogenic non-epileptic seizures or dissociative seizures, present with ictal semiologial manifestations, along with various comorbid neurological and psychological disorders. Terminology inconsistencies and discrepancies in nomenclatures of FS may reflect limitations in understanding the neuropsychiatric intricacies of this disorder. Psychological and neurobiological processes of FS are incompletely understood. Nevertheless, important advances have been made on underlying neuropsychopathophysiological mechanisms of FS. These advances provide valuable information about the underlying mechanisms of mind–body interactions.

**Method:** From this perspective, this narrative review summarises recent studies about aetiopathogenesis of FS at two levels: possible risk factors (why) and different aetiopathogenic models of FS (how).

**Results:** We divided possible risk factors for FS into three categories, namely neurobiological, psychological and cognitive risk factors. We also presented different models of FS based on psychological and neuroanatomical understanding, multilevel models and integrative understanding of FS.

**Conclusion:** This work should help professionals to better understand current views on the multifactorial mechanisms involved in the development of FS. Shedding light on the different FS profiles in terms of aetiopathogenesis will help guide how best to direct therapy, based on these different underlying mechanisms.

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Translation and validation of the Russian-language version of the brief Epilepsy Anxiety Survey Instrument

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Purpose: Patients with epilepsy (PWE) are more likely to develop anxiety disorders compared to the general population, with the prevalence rate about 20.2% (Scott A et al., Epilepsia 2017, 58(6):973-982). Epilepsy Anxiety Survey Instrument (EASI) was recently developed precisely for PWE (Scott A et al., Epilepsia 2019, 60(10):2068-2077) and is now recommended by the ILAE. The short version of the tool (brEASI) could be particularly well suited to busy neurology settings where rapid, accurate, and cost-effective screening for psychiatric comorbidity is warranted. The brEASI has never been validated in the Russian-language population.

We aimed to investigate the psychometric properties of the Russian-language version of the brEASI.

Method: A psychiatrist, fluent in English and Russian, provided translation from English into Russian, and another performed blind back-translation from Russian into English. One of the inventory authors reviewed the back-translated version of the EASI/brEASI. A consecutive cohort of PWE was assessed with the brEASI and Mini International Neuropsychiatric Interview (M.I.N.I.) module for panic disorder, agoraphobia, social anxiety disorder and general anxiety disorder. Receiver operating characteristic (ROC) analyses for the brEASI scores, identifying higher Yuden’s index, were used as a statistical method.

Results: The cohort consisted of 181 PWE: 118 (65.2%) females; mean age was 39.6 (14.6); 152 (84.0%) had focal epilepsy; mean age at onset of the epilepsy was 22.4 (16.1). According to M.I.N.I., one-third (33.7%) of patients had any anxiety disorder. An area under the curve (AUC) for any anxiety disorder was 0.916 (95%CI 0.866-0.952). At the cutoff point >7 the brEASI had a sensitivity of 83.61% (95% CI 71.9–91.8%), a specificity of 92.5% (95% CI 86.2–96.5%), a positive predictive value of 73.8% (59.9–84.2), a negative predictive value of 93.2% (90.6–95.1).

Conclusion: The Russian-language version of brEASI is an effective screening tool for detecting anxiety disorders in PWE.

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Previous suicide attempts by patients with psychogenic seizures have been associated with depression and suicidal crises in inpatient treatment

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Purpose: Suicide attempts (SA) are emergencies in patients with psychogenic seizures (PS). We therefore analyzed how these patients with (PWSA) and without SA (PWOSA) differ.

Method: The patients were examined with SDQ-20, CTQ, TEC, FDS, BDI, SCL90-R and SKID. Acute and latent suicidality, previous SA and high-risk behavior were also asked. Statistical comparison of the two groups was carried out using the Fischer-Yates test.

Results: Of 49 patients (40 women, 9 men), 24.5% (9 women, 3 men) reported at least 1 SA (1-5) in the past. Median age was 29.5 (18-65) for PWSA versus 38 (18-67) years for PWOSA. The PWSA showed significantly more often (p <0.05) at least moderate depression (75% versus 40.5%), suicidal crises in the context of inpatient treatment (50% versus 2.7%), and high-risk behavior in everyday life (33.3% versus 0%).

No significant differences were found for PTSD, phobias, anxiety disorder, substance abuse, eating disorders, artificial seizures, epilepsy, learning disability, dissociative symptoms, ADHD, personality disorders, organic delusional disorders, acute stress response and OCD.

Conclusion: Lifetime prevalence of SA is estimated at approx. 9%⁴. It is significantly higher in our patients (24.5%) and comparable to other reports (25%⁴ and 32%⁵). The higher number of suicidal crises in the context of inpatient treatment of PWSA compared to PWOSA supports the assumption of Dworetzky⁶ that previous suicide attempts and at least moderate depression are a risk factor for further suicidal crises in these patients and should be monitored carefully.

Literature:
Post-traumatic stress disorder symptoms (PTSD) related to brain PET hypometabolism in patients with temporal lobe epilepsy

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Purpose: Anxiety and depression in epilepsy are strongly documented but post-traumatic stress disorder (PTSD) is underestimated and poorly known. We studied the relationships between psycho-traumagenic exposure and PTSD symptoms in patients with epilepsy. Secondly, we aimed to determine the metabolic characteristics associated with PTSD in temporal lobe epilepsy (TLE).

Method: We included 39 patients with drug resistant TLE having presurgical evaluation in our department. We used validated questionnaires to assess anxiety, depression, and PTSD symptoms and an original exploratory questionnaire for screening for PTSD during interictal and peri-ictal periods. We compared the differences in brain PET metabolism between patients with TLE and PTSD (TLE-PTSD+, \(N=15\)), patients with TLE without PTSD (TLE-PTSD-, \(N=24\)) and healthy control group (\(N=30\)), and their correlation with interictal and peri-ictal scales of PTSD symptoms scores.

Results: Patients reported more exposure to a psycho-traumagenic event (78% vs. 52%) and presented significantly more severe PTSD symptoms than controls (26% vs. 7%). The PTSD scores of the two groups of epileptic patients combined was correlated to PTSD symptoms during the ictal and peri-ictal periods. Moreover, TLE-PTSD+ showed more significant hypometabolism involving the right temporal pole, including its medial limbic part, and the orbito-frontal cortex region in comparison to TLE-PTSD- patients and to healthy participants. Moreover, reduced metabolism in these brain areas was correlated with the diagnostic PTSD questionnaire and the PTSD scale measuring epilepsy-specific PTSD symptoms in the peri-/inter-ictal period.

Conclusion: Patients with epilepsy have increased prevalence of self-reported PTSD symptoms and present a specific PTSD clinical picture characterized by PTSD symptoms during inter and peri-ictal period. Moreover, PTSD in temporal epilepsy appears associated with specific changes in neural networks, affecting limbic and paralimbic structures. This highlights the close intertwining of epileptogenesis and psychogenesis processes.

Gender differences in the comorbidity of mood disorders in neurosurgical patients

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Purpose: Affective disorders were the most common comorbid disorders in epilepsy. The objective of this study was the gender epidemiology of affective disorders among neurosurgical patients with drug resistant epilepsy.

Method: 46 neurosurgical patients with pharmacoresistant epilepsy were divided into two groups: males (group1) and females (group2). Demographic and clinical parameters were examined. Hospital Anxiety and Depression Scales (HADS), Generalized Anxiety Disorder Scale (GAD-7), and Beck’s Depression Inventory were used for testing. All patients completed informed consent forms. We used descriptive statistics.

Results: Group1 included 28 patients (61%), group2 – 18 (39%). The average age was 31.4 years, with no differences between groups. Male-to-female ratio = 1.5:1. The average duration of the disease was 19.6 years. HADS (anxiety): normal - 74% in group1 and 61% - group2; subclinical – 11% and 17%; clinically significant - 18% and 22%, respectively.

HADS (depression): normal - 82% in group1 and 67% - group2; subclinical - 11% and 22%; clinically significant -7% and 11%.

GTR-7: mild anxiety - 57% in group2 and 50% - group2; moderate - 25% and 11%; severe - 7% and 33%; severe and panic level - 11% and 6%.

Beck’s Depression Inventory: considered normal - 50% in group1 and 44% - group2; borderline clinical depression – 32% and 28%; mild mood disturbance – 7% and 5.5%; moderate – 7% and 11%; severe – 3.5% and 11%, respectively.

Conclusion: There was a prevalence of patients with a minimum level of anxiety and the absence of symptoms of depression in both groups, regardless of gender, it can be concluded the gender differences in the emotional sphere in neurosurgical patients were smoothed out due to long duration pharmacoresistant epilepsy.
Epilepsy and employment: classification of workplaces and optimized legislation in Austria – a qualitative study

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Purpose: People with epilepsy (PWE) face difficulties in obtaining or keeping employment. The question whether epilepsy must be disclosed during the application process is of central importance. In extreme cases, PWE can be dismissed under the term of violation of confidence.

Method: Twelve personnel managers and five occupational health practitioners underwent a telephone interview concerning the opportunities and limitations of job applications by PWE in Austria. The interviews were analyzed by the qualitative method of content analysis (Kuckartz). The legal situation was also analyzed.

Results: Employers were confident that co-workers with epilepsy could be managemed well if a value system and statutory first responders were in place. The Austrian law allows only retrospective juridical clarification of the questions asked by employers during the application process. Applicants often cannot afford a time-consuming and expensive lawsuit. The authors developed a classification system for work places with “D-0” (“D null”) meaning no health or financial danger (e.g. office workers). “D-1” poses still no health hazard but includes regular work with cash (e.g. salespersons). Employers may downgrade D1 to conditions of D0 (“D1-0”, “D-one-null”). “D-2” implies potential medical hazard for any person at the workplace including PWE (e.g. industrial worker). With D2, occupational health practitioners evaluate the applicant’s medical fitness for the job without disclosing medical details. Employers may only focus on qualifications. The D-system is part of the job advertisement to encourage PWE to apply. PWE have pure conscience to keep their epilepsies a secret in each D-category. In particular, PWE need not be afraid to lose their jobs if their epilepsies were disclosed by accident.

Conclusion: We present a practical and simple classification of workplaces and a concept for keeping medical information confidential during application. These measures may diminish enacted and felt stigma in the working world.

Awareness about epilepsy among the medical students in Kyrgyzstan

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Purpose: To reveal the awareness and attitude of young people in Bishkek to this disease.

Methods: The study included 85 medical students, aged 18 to 26 years, the average age was 22 ± 1.76 (34men, 51women). The main assessment method was a questionnaire survey, consisted of 20 questions.

Results: It was revealed that 92.9% of the students know about epilepsy. Only 37.6% of them directly saw an epileptic seizure. 49.4% of students recommended to open their jaws with a hard object and perform „artificial respiration” (3.5%), and only 51.7% would be able to provide correct first aid. All interviewed students knew that epilepsy cannot be contaminated from patients. However, only 49.4% knew that genetic factors can cause epilepsy, and 68.8% did not know that alcohol, drug use, smoking, constant work at the computer, watching TV and disturbed sleep and rest can trigger an epileptic seizure. Unfortunately, they believe that children with epilepsy can attend educational institutions only with the permission of other parents (40%) and 57.6% of them expressed a desire to study and work with this category of patients. 82.3% of students believe that patients are not prone to aggression, violence and they do not have a decrease in intelligence. 52.9% assume that it is more difficult for these patients to get a job, and therefore they have to hide their diagnosis. The majority of young people (53%) still believe that alternative medicine is one of the effective methods of treatment. Only 23.5% of those surveyed believed that epilepsy could be a curable disease and that patients should take antiepileptic drugs.

Conclusions: Most negative perceptions were significantly associated with misconceptions about epilepsy. It is necessary to continue the effective implementation of educational programs to improve knowledge and beliefs about epilepsy, in order to reduce social discrimination patients with epilepsy.
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Epilepsy on my mind: the caregivers’ perspective

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Purpose: Epilepsy can carry neurological, cognitive, psychological, and social consequences that can impose significant burdens not only on those affected but also on their families or other carers. We wondered to which degree carers felt that epilepsy had an impact on their life.

Methods: We performed a web-based survey among caregivers and family members of persons with epilepsy (PWE). They were asked to which degree they were thinking about the person’s epilepsy in daily life, to which degree they were afraid for the PWE to get a seizure and to which degree the person’s epilepsy was influencing their (the carers) daily life.

Results: 908 Carers participated. 23.8% of PWE were reported to have been seizurefree for at least 12 month and 22.8 had monthly seizures. The majority (70.2%) of carers reported to be thinking about person’s epilepsy in daily life to a large degree, 52% of carers reported to be afraid for the PWE to get a seizure to a large degree and the impact of the person’s epilepsy on the carers daily life was rated to have a high degree by 58%. Factors associated with a high impact were not being seizure free, having tonic-clonic seizures, and using polytherapy. However having been informed on the risk for epilepsy related injuries or death did not increased the impact on the caregivers.

Conclusions: In this population-based survey we found that a clear majority of caregivers, family members or custodians of PWE reported that they were thinking about the person’s epilepsy, that they were afraid for seizures and that their own daily life was influenced to a large degree by the person’s epilepsy. This survey underlines that not only the PWE but also the persons around them have to cope with the burden of epilepsy.

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Adapted physical activity reference for people with epilepsy: first french guidelines

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Purpose: Even though physical activity has shown many benefits on epilepsy and can be prescribed by physicians, currently there is no promoted recommendations in France. In order to encourage this practice among people with epilepsy, the La Teppe Institute coordinated the drafting of a collective expertise on physical activity adapted to this pathology.

Method: Following a national call for participation, 34 contributors working in the field of epilepsy from different disciplines [neurology, adapted physical activities, high-level sport, sociology, philosophy, anthropology and Literature] throughout France agreed to take part in this project. These different areas of expertise give to this work an interdisciplinary perspective.

Results: This collective expertise will be published in June 2022. The guidelines are divided into three parts [neurology, adapted physical activity and social sciences] which allow to identify the benefits of physical activity on epilepsy, the safety supervision techniques for professionals and the processes of motivation and commitment for practitioners.

Conclusion: This work should help professionals and people with epilepsy to better understand the role of physical activity on this disease and how practice it safely and securely. The distribution and application of these guidelines especially to the health facilities specialized in epilepsy remain currently our main challenge.
What is known from existing literature about stigma in functional seizures: a scoping review

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Purpose: The purpose of this scoping review was to explore the extent, range and nature of knowledge on stigma in functional seizures (FS).

Methods: This scoping review was conducted in accordance with the Joanna Briggs Institute Manual for Evidence Synthesis (JBIMES) guidelines and the five-step framework by Arksey and O'Malley. We searched for data sources written in English using MEDLINE, Scopus, EBSCOhost, Ovid, PubMed, Science Direct, Web of Science, Wiley Online Library, Microsoft Academic, Google Scholar, as well as grey literature sources, with no date limitations up to September 2021. The extracted data were analyzed using basic frequency counts and thematic analysis.

Results: The systematic search yielded a set of 988 relevant data sources, of which 70 met the inclusion criteria. The retrieved sources reflected data from 85 countries and 5949 study participants. The thematic analysis highlighted the prevalence of FS stigma, as well as its potential origins, context and impact on patients and families. The majority of studies were conducted in healthcare settings with healthcare providers, with fewer data sources reporting on family, patient, and broader society perspectives relating to FS stigma.

Conclusion: Our scoping review revealed that although the field of FS stigma remains understudied and under reported, from what we do know, stigma in FS is prevalent in many contexts across the globe. Healthcare providers, families, caregivers, significant others and FS patients themselves often hold stigmatizing perceptions and attitudes towards FS. We need more research with a specific focus on stigma in FS, and factors that contribute to FS stigma (e.g. culture and context, naming of the condition), as well as accessible interventions and guidelines addressing FS stigma through education and training. Supportive attitudes and knowledge appears to be protective factors against FS stigma.

Understanding the journey of Dravet syndrome patients and their families: a qualitative study of their lived experience

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Purpose: Dravet syndrome (DS) is a rare treatment-resistant developmental epileptic encephalopathy characterised by multiple types of frequent, disabling seizures that develops in infancy. Previous research has focused on the clinical impact of DS. This research aimed to explore the impact of DS on the experiences of the whole family.

Method: In this qualitative study, 43 families, from 5 European countries, were interviewed via telephone and video conference. The ages of the children and young adults with DS ranged from 15 months to 23 years, and severity of DS ranged from mild to severe. Interpretative Phenomenological Analysis was used to analyse the data for emerging themes.

Results: Early conversations surrounding DS are the most memorable and impactful for families as their experience at diagnosis can set the direction for the journey ahead. Early experiences in the treatment journey can have a significant, long-lasting effect on caregivers' anxiety levels and their future attitudes to treatment decisions. Caregivers report being fearful of trying new or higher doses of drug therapies because of the potential side effects. Transitional milestones in the journey require families to continually adapt to different sets of challenges, particularly around starting school, puberty, and adulthood.

Conclusion: This study highlighted that DS has a significant impact on the lives of patients and their families. Healthcare professionals have an opportunity to positively impact on families' journeys around the key milestones identified above. Acknowledgement of the wider aspects of DS and facilitation of shared decision making would give agency to families as they balance quality of life and developmental issues with seizure management. This research was funded by Zogenix International Ltd.
Current situation and issues of Japanese university health centers in supporting university students with epilepsy

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Purpose: Students with epilepsy often require support for health management and daily activities. In this study, we investigated how university health centers provide students with epilepsy with medical care and advice on dealing with associated issues at school and in their daily lives.

Method: We conducted a self-administered, anonymous questionnaire survey of managers of university health centers at 506 member universities of the Japan University Health Association.

Results: In total, 203 centers returned the questionnaires (response rate: 40.1%). Among them, 165 centers (81.3%) had experience of providing support for students with epilepsy. Most centers reported that the students themselves came to the center to ask for a consultation (114/165 centers, 69.1%), and they sought advice on what they should do if they have a seizure (97 cases, 58.8%) or requested information on treatment of epilepsy or referrals to medical institutions (61 cases, 37.0%). In the past 5 years, 122/203 centers (60.1%) had helped students who had a seizure; each center had helped a mean of 4.3 students in that period. Seizures occurred during classes in 87 cases (70.2%). The health centers contacted the student’s parents (94 cases, 75.8%), called an ambulance to take the student to a hospital (86 cases, 69.4%), or took the student to the health center (76 cases, 61.3%). In addition, a total of 87/203 centers (42.9%) had experience of being contacted by teachers for advice on students with epilepsy. Most teachers wanted to learn what they should do if a student had a seizure (69 cases, 79.3%).

Conclusion: Many students with epilepsy use university health centers to receive advice. University health centers can play an important role in improving the school life of students with epilepsy and providing/sharing information with teachers. This research was supported by JSPS KAKENHI Grant Number 18K02791.
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Epilepsy stigma perception of medical students in Albania

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Purpose: To estimate perceived stigma towards epilepsy in medical students in a transitional South-Eastern European country.

Methods: In our cross-sectional study a random sample of medical students at the Faculty of Medicine, University of Medicine, were interviewed by neurology specialists and residents employing the previously validated version in Albanian of the Stigma Scale in Epilepsy (SSE). The SSE score, including every single epilepsy stigma domain, vary from 0 (no stigma) to 100 (total stigma). Moreover, demographics, data on family and friends with epilepsy and a personal statement on epilepsy stigma were recorded.

Results: In total, 376 medical students (81.8% females) with a mean age of 20.7 ± 1.9 years were included in the final analysis after discarding 17 incomplete questionnaires. 9.4% and 41.4% had respectively at least one family member or friend with epilepsy. Existence of stigma towards people with epilepsy was acknowledged by 41.8% of the students. The mean SSE score resulted 46.5 ± 14.4. In the social and personal epilepsy stigma domains the mean scores were respectively 45.8 ± 18.2 and 48.1 ± 17.5. Males and females showed no statistically significant differences in scores. Students that acknowledged the epilepsy stigma scored higher in total SSE score (53.2±12.5 vs. 41.7±13.8, p <0.001), social stigma score (54.6±16.3 vs. 39.6± 17.0, p <0.001) and personal stigma score (53.8±16.0 vs. 44.1±17.5, p <0.001). Likewise, in multivariate linear regression analysis stigma acknowledgement was positively associated with higher total SSE score (β 11.40, 95%CI 8.62-14.18, p <0.001), social stigma score (β 14.66, 95%CI 11.18-18.13, p <0.001) and personal stigma score (β 9.46, 95%CI 5.95-12.96, p <0.001) after adjusting for age, gender, year of study, residency location, and family members or friends with epilepsy.

Conclusion: Epilepsy stigma is highly perceived by medical students recognizing that epilepsy is frequently accompanied by psychosocial difficulties in Albania.

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Do Montenegrin students of non-medical faculties have a lack of knowledge regarding epilepsy?

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Purpose: People with epilepsy face stigma which arguably causes more suffering than the disease itself. The aim of this study was to evaluate and compare the knowledge about epilepsy amongst students of non-medical faculties in Montenegro.

Method: This study was performed during March 2022. Descriptive statistical analysis was used.

Results: A total of 450 questionnaires were distributed; the response rate was 91.2%. There were 267 (64.97%) female respondents. Epilepsy was regarded as a neurological disease by 89.59% of students. The rank of causes of epilepsy given by respondents was brain injury (73.24%), tumors (65.23%), stroke (63.26%), high fever (9.98%), headache (16.06%), depression (16.79%), alcoholism (9.49%). About 77% of respondents would call emergency if they were present during seizure, while 29,3% of them would protect head of patient in that situation. 63% of respondents think that epilepsy patients have working disabilities. Most of our respondents (65%) think that having epilepsy is a risk for developing dementia while about 44% of them think that sports activities should be forbidden for epilepsy patients. Four percent of students strongly agree that patients suffering from epilepsy should not have children, while 10% of respondents think that they die earlier compared with healthy population. Every third respondent would never have a relationship and 37% of them would never marry a person suffering from epilepsy. As an employer, 8.7% of students would not give a job to person suffering from epilepsy. About 5% of respondents would not let their children play with a child suffering from epilepsy.

Conclusion: There is a lack of knowledge about epilepsy in our study group. Therefore, universities are required to improve the knowledge of students about epilepsy by integrating education and first aid course into curriculum. Also, it is necessary to reduce negative attitudes by public education campaigns.
Status Epilepticus

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Review of the new Advanced Paediatric Life Support guideline (2021): management of the convulsing child

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Convulsive status epilepticus (CSE) is the most common childhood medical neurological emergency. A convulsion lasting more than 5 minutes is considered prolonged and will often require treatment to aid termination. If a convulsion persists beyond 30 minutes, it is associated with increased risk of death and long-term neurological consequences. However, the main predictor of outcome is the underlying aetiology. The duration of the convulsion is also important with medical treatments, particularly benzodiazepines, becoming less effective with increasing duration. Effective early intervention is crucial to outcome. The proposed guideline is set to provide an updated evidence-based structured approach on how to manage the convulsing child in the United Kingdom.

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Rate of occurrence of non-convulsive status epilepticus in general neurological clinic: a retrospective study of 96 patients

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Purpose: The estimation of the rate of occurrence of Non-Convulsive Status Epilepticus (NCSE) in a sample of inpatients with altered mental status and the evaluation of the outcome of NCSE in relation to underlying cause, imaging, comorbidity, age and complications.

Method: EEG, clinical and paraclinical features of 96 patients who had been hospitalized for altered mental status over the past 4 years at the 2nd Neurologic Department and the interconnected Internal Medicine Department of AHEPA University Hospital were retrospectively evaluated.

Results:
3. Patients with poor outcome (5pts): Mean age: 76. Causes: acute cardio-respiratory deficiency, hydrocephalus and edema of cerebral cortex due to ventriculoperitoneal shunt (VPS) complications, possible encephalitis, meningeal carcinomatosis, stroke with temporal lobe edema. Complications: systemic infections in 4 cases. Mean hospitalization prior to death: 25.6 days. 2nd line treatment with 3 AEDs in 3 cases.

Conclusion: Poor outcome is associated with high age, neoplasia, stroke and VPS complications, encephalitis, complications after cardio-respiratory deficiency and also, in high proportion (4/5), with systemic infections and prolonged hospitalization. The results are in agreement with the literature data, demonstrating that high age, serious etiology and complication with systematic infection are high risk factors directly related to mortality.
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Febrile infection-related epilepsy syndrome: tailoring an approach to treatment

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Purpose: A dysimmune process has been thought to underlie Febrile Infection-Related Epilepsy Syndrome (FIRES). Cytokine profiling prior to immunotherapy in FIRES is increasingly prevalent. However, serial profiling and tailoring of multiple immunotherapeutic agents to a changing immunologic profile is rarely performed. We describe our experience with directed immunotherapeutics in a patient with FIRES.

Methods/Results: An 18-year-old boy presented with first-onset seizure a week after a nonspecific febrile illness. He developed refractory seizures requiring multiple anti-seizure medications and general anesthetic infusions. He was treated with pulsed methylprednisolone, plasma exchange and ketogenic diet. Contrasted brain MRI showed post-ictal changes. EEG showed multifocal ictal runs and generalized periodic epileptiform discharges. Cerebrospinal fluid analysis, autoantibody testing and malignancy screen were unremarkable. Genetic testing showed variants of unknown significance in the CNKSR2 and OPN1LW genes.

Initial serum and CSF cytokine analyses revealed that INFg, IL-6, IL-10 and TNFa were highly activated predominantly in the CNS, consistent with macrophage activation syndrome. Tofacitinib was initially trialed in view of the elevated IFNg suggesting increased T and NK cell activity and potentially superior CNS penetration. After 3 weeks of tofacitinib, there was no significant clinical improvement. Our patient had developed nosocomial infections and significant suppression of multiple cytokines other than those of macrophage activation syndrome. However, IL-6 continued to rise. He was switched to tocilizumab with significant electrophrographical improvement. Anakinra was also given because of persistent prolonged ictal activity after 4 doses of tocilizumab but subsequently stopped because of lack of clinical response.

Serial cytokine profiling showed improvement and subsequent near-normalization of cytokine levels after 7 doses of tocilizumab. There was corresponding improved seizure control. Currently, at 6 months after his initial presentation, he is undergoing rehabilitation with gradual down-titration of his anti-seizure medications.

Conclusion: This case illustrates how personalized immunomonitoring may potentially be helpful in cases of refractory epilepsy.

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Role of Ocimum sanctum extract on seizure control and neuroprotection in status epilepticus model in rats in comparison with valproate

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Purpose: Status epilepticus (SE) causes prolonged or repetitive seizures that, if left untreated, can lead to neuronal injury. Ocimum sanctum L., a well known Ayurveda medicine has shown promising neuromodulatory effect including epilepsy. Herein the impact of Ocimum sanctum hydroalcoholic extract (OSHE) alone and in combination with valproate (VPA) has been investigated in SE model in rats.

Method: Animals received 127 mg/kg LiCl followed by pilocarpine (25 mg/kg) 24 h later for induction of SE. OSHE (1000 mg/kg) and VPA (370 mg/kg) were administered alone or combination for 3 days prior and 14 days post SE induction. Seizure parameters were recorded on day 1(0-3 hr), day 1-3 and day 4-14. Neurobehavioral changes, total antioxidant capacity (TAC), Neuron-specific enolase (NSE) in cerebral cortex and hippocampal histopathology (electron-microscopic) were assessed at day 14.

Results: Seizure protection (% of rats without stage 3/4 seizures) was more in OSHE+VPA group (75%) than other groups (VPA-66.7%, OSHE-58.3%, SE control-8.3%). The time latency increased and number of stage 3/4 seizures reduced in all drug treated groups vs. SE control group (p<0.001). OSHE+VPA group (p<0.001) had better memory retention than all other treated groups as evident from passive avoidance test but not in elevated plus maze test. OSHE+VPA group had significantly higher TAC (21.77±3.12; p=0.008) and NSE (9.28±1.30; p=0.01) as compared to SE control. Electron-microscopy changes showed significant hippocampal myelin sheath damage (62.9%, p<0.001) and axonal degeneration (37.7%, p<0.05) in SE control compared to all drug treated groups

Conclusion: OSHE has comparable seizure control and neuroprotection as with valproate. OSHE+VPA showed higher seizure protection and memory retention than valproate alone.
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Treatment of prehospital status epilepticus with intravenous anaesthetic drugs - Do they really increase mortality?

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Purpose: We performed this retrospective data bank analysis to evaluate the risks and benefits of treatment of prehospital status epilepticus (SE) with intravenous anaesthetic drugs (IVAD).

Methods: We evaluated all treatment episodes of a prehospital SE according to our hospital record system between January 1st 2014 and December 31st 2018. Classification according to the International League Against Epilepsy (ILAE) classification of 2015, Status Epilepticus Severity Score (STESS), Charlson Comorbidity Index (CCI) at admission and the modified Rankin Scale (mRS) at discharge or in hospital death were recorded. Statistical analysis was performed with the t-test, the Mann-Withney-U test and the Chi-Square test.

Results: In 41 patient treatment episodes with IVAD nine patients (22%) died, rendering an increased mortality in comparison of treatment episodes without use of IVAD (odds ratio 4.8; 95% CI 2-11.8, p < 0.001). Especially CCI was higher in patients who died after treatment with IVAD than in those who survived after this treatment (median 6, IQR 4-7 vs. median 1, IQR 1-2, p < 0.0001). There was a trend for lower mortality when IVAD was started in the prehospital setting (10% vs. 33%, odd-ratio 0.22 95% CI 0.04-1.2 p = 0.07).

Conclusion: The association of mortality with IVAD treatment in prehospital status epilepticus may be at least partially a result of reduced general condition due to comorbidities. Early treatment with IVAD may even lead to lower mortality.

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The role of the EEG in predicting 30-day mortality after status epilepticus

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Purpose: The Status Epilepticus Severity Score (STESS) appears particularly accurate and effective in identifying patients with 30-day survival (high negative predictive value). Its predictive value for 30-day mortality is lower and needs to be further implemented. We used reclassification improvement analysis to evaluate whether the inclusion of data on electroencephalographic (EEG) patterns improves the predictive value of STESS.

Method: We included consecutive episodes of SE in patients aged ≥14 at Modena Academic Hospital. Through reclassification improvement analysis, we evaluated whether adding EEG data to STESS variables could improve the predictive capacity of this score. Spontaneous burst-suppression, after status ictal discharges, and periodic lateralized or generalized EEG discharges were compared to EEG patterns without these abnormalities. The outcome was 30-day mortality. Net reclassification improvement (NRI) was used to quantify the accuracy of the EEG+STESS model in reclassifying the risk of mortality compared to STESS alone.

Results: 711 patients with SE were included, with a 30-days mortality of 28.1% (200/711). The median STESS in the entire population was 3 (interquartile range IQR, 2-5). Compared to STESS variables alone, the inclusion of EEG data improved the capability of this score in predicting 30-day mortality by a NRI index of 23.3% (SD 0.05, p <0.001). In patients who died within 30 days, the EEG did not increase the predictive capacity of STESS. In surviving patients, the EEG improved the predictive potential of STESS in 36.1% of patients (184/509).

Conclusions: Adding the EEG to STESS variables further increases its effectiveness in identifying patients with 30-day survival, whereas it does not seem to add significant information to identify patients with 30-day mortality. Further studies are required to corroborate these findings, and to investigate whether specific EEG patterns can accurately predict 30-day mortality following SE. Effectively predicting 30-day mortality after SE remains an unsolved and challenging issue.
First description of lingual focal motor status epilepticus due to ischemic stroke

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Purpose: Focal motor status epilepticus (SE) involving one half of the tongue is exceptionally rare, diagnostically challenging, and so far never described in the context of an acute stroke. We describe a case of lingual SE due to ischemic stroke, providing suggestions for diagnostic workup.

Methods: Case report.

Results: A 82-year old man was admitted for sudden onset of right hemiparesis and motor aphasia due to acute ischemic stroke. His medical history was significant for arterial hypertension, hypercholesterolemia, hypothyroidism; he was taking warfarin for prior pulmonary embolism. Neither systemic thrombolysis (high INR values) nor thrombectomy (no large vessel occlusion on cerebral angi-CT) were performed. Three days later, he presented with subcontinuous clonic movements affecting the right side of the tongue, without palatal tremor or impaired awareness. The video-EEG showed massive muscle artifacts, without epileptiform abnormalities, rhythmic patterns or focal slowings; the brain MRI showed left frontal ischaemia. Levetiracetam 500 mg X 2 was administered orally with cessation of the SE.

Conclusions: Lingual SE is extremely rare and so far never described as a consequence of a stroke. It reflects the activation of the cortical tongue representation in the contralateral primary motor cortex (epileptogenic zone). In this condition, clonic movements are not usually associated with a clear ictal pattern in the EEG. In our case, the semiology and response to levetiracetam supported the diagnosis of SE. Although exceptionally rare, clinicians should be aware of lingual SE. Semiology, correlation with neuroimaging, video-EEG (although not usually informative due to the absence of EEG abnormalities and the marked muscle artifacts) and ex juvantibus therapy with antiseizure medications should be carefully considered to differentiate this conditions from non-epileptic lingual myoclonus due to brainstem lesions (symptomatic myoclonus) or without an identifiable cause (essential myoclonus). Interpretation within the clinical context is mandatory to reach the diagnosis.

“It’s not mine!” First description of non-convulsive status epilepticus manifesting with somatoparaphrenia

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Purpose: Somatoparaphrenia is a delusion characterized by the denial of ownership for a limb or an entire side of body. It is associated with lesions in the right hemisphere, and often accompanied by left-sided paralysis and anosognosia. We describe a case of non-convulsive status epilepticus (NCSE) presenting with somatoparaphrenia. No prior case of somatoparaphrenia in SE has been reported.

Methods: Case report.

Results: A 86-year old, right-handed woman presented with clonic movements in her left upper limb and half of the face, with head and eyes deviation towards the left. Her medical history was significant for previous ischemic stroke in the right middle-cerebral artery territory; arterial hypertension; previous breast and ovarian cancers. The symptoms ceased following intravenous administration of benzodiazepines. The CT (repeated after 48 hours) showed no acute ischemic lesions. After three days, the patient had mirror hand movements with grasping reflex on the left hand; strength and language were normal, without motor phenomena suggesting seizures. Results of head CT were comparable with prior examinations, whereas the perfusion-CT showed right-sided fronto-temporal hyperperfusion (increased regional cerebral-blood volume). The patient was unable to recognize the left arm as her own (instead, she consistently attributed it to the visiting physician), without concomitant paralysis or anosognosia. The EEG showed a pattern of epileptiform discharges on right centro-temporal regions, compatible with NCSE. Diazepam, valproate and lacosamide were unable to control SE. The patient became rapidly unresponsive and vital parameters deteriorated until death.

Conclusions: The most striking symptom of NCSE in this patients was the delusional belief that the left arm did not belong to her. Clinical, neurophysiological and neuroimaging data point to symptoms arising from a right (non-dominant hemisphere) fronto-parietal epileptogenic zone. Although extremely rare, even more as an epileptic symptom, somatoparaphrenia should be promptly recognized for its localizing value.
Exploratory study of new serum microRNAs related to the diagnosis of Status Epilepticus (SE)

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Purpose: Blood levels of a number of microRNAs have been reported to be altered in rodent models and in patients with epilepsy. The aim of this study was to explore microRNA expression profiles in the serum of patients with SE at emergency department (ED) arrival to explore their role as potential diagnostic biomarkers; in addition, we wanted to describe which biological processes are involved in those mRNAs with different expression in SE.

Method: Of a prospective database of patients with suspected epileptic seizures, in which serum samples were collected on arrival at the ED, we selected samples from 8 patients with a final diagnosis of SE and 8 patients with no SE criteria matched by age, sex and seizure aetiology. In these samples, a microRNA profiling was performed.

Results: A total of 2,578 mature human microRNAs were analysed. In the analysis of differentially expressed miRNAs, there are a total of 41 with a p-value <0.01 (unadjusted) to differentiate between SE and controls, 19 overexpressed and 21 with a low level of expression in SE. For candidate analysis, we selected the 3 most overexpressed miRNAs and the 3 most significant miRNAs with a foldchange >1. We obtained a total of 5 miRNAs: hsa-miR-6852-5p, hsa-miR-1910-3p, hsa-miR-129-5p, hsa-miR-6851-5p, hsa-miR-6754-3p. One of the gene targets of the first 3 is SVOP: SV2 related protein, that may play an important role in modulating nervous system excitability. Other targets of these microRNA include posttranscriptional regulation of gene expression, programmed cell death mechanisms, such as p53 activation; and tissue remodeling.

Conclusion: miRNA screening allows the discovery of new serum candidates associated with SE. These microRNA might support differential diagnosis of SE from other emergent situations mimicking prolonged seizures.

Status epilepticus in mesial temporal lobe epilepsy

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Purpose: Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis (MTLE-HS) is the prototype of drug resistant epilepsy but little attention has been paid to status epilepticus (SE) in this constellation. We aimed to explore the differentiating characteristics of this situation.

Method: We retrospectively reviewed the data of 116 patients with MTLE-HS, diagnosed according to their clinical and neuroimaging features, who were followed by the epilepsy outpatient with a follow-up duration of 16.7±7.1 years. Data were collected from the files, MRI and EEG archives to delineate the history of status epilepticus, clinical features and laboratory characteristics.

Results: There were 18 patients (16 females) with SE in the main group and the remaining 98 patients (53 females (p=0.08)) without SE served as the control group. 10 patients had convulsive SE, 7 non-convulsive SE and 1 aura continua.

Frequency of seizures(p=0.000), age at seizure onset (p=0.000), history of generalized tonic-clonic seizures(GTCS) (p=0.031), mental retardation(p=0.000), and psychosis(p=0.03) were all higher in the SE group. Moreover, bilateral HS issignificantly higher (p=0.04) in the SE group. The seropositivity ratio for anti-neuronal antibodies is also higher in the SE group (7/11 versus 19/93) (p=0.00). Engel 1 rate after surgery was lower in patients with SE (4/11) than patients without SE (43/49) (p=0.01). There were no significant differences between two groups according to age, history of febrile seizures, psychiatric disturbance, family history of epilepsy, additional focus, back ground activity on the EEG and sleep-related seizures.

Conclusion: Female patients with MTLE-HS with more frequent seizures, history of GTCS, mental retardation, psychosis and bilateral HS along with anti-neuronal antibodies and unfavorable results of epilepsy surgery are at higher risk of SE for yet unexplained reasons. Our preliminary findings indicated a subgroup with a different pathophysiological background among the MTLE-HS group, associated with SE risk.
380 European standards of steroid therapy in children with electrical status epilepticus during sleep (ESES)

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**Purpose:** ESES is a rare but well-known childhood epileptic disorder. There is no uniform approach to treatment. The aim of this project was to evaluate the different regimens of steroid treatment for epilepsy with electrical status epilepticus in sleep (ESES) at different centers across Europe.

**Method:** An online survey was conducted (via ‘SurveyMonkey’ Europe) and distributed among pediatric epileptologist of European epilepsy centers. Questions focused on center, ESES definition, and regional/national guidelines for diagnostic and therapeutic management of ESES. Particular attention was paid to the indication/contraindication of steroids and treatment regimens used.

**Results:** We received responses of 49 centers (by January 2022). Local standard operating procedures were available in 49%, national guidelines in only 26% of centers. Definitions applied vary with respect to both clinical manifestations and sleep EEG characteristics. Overall, clonazepam and steroids were the two most commonly applied treatment options. Indications for steroids were primarily neurocognitive arrest (53%) and clonazepam failure (55%); but in 26% ESES recording in the absence of neurodevelopmental deficit was regarded as an indication for steroids. Treatment goals for steroids were mainly neurodevelopmental improvement (96%) and improvement of behavioral disturbances (70%). However, 62% aimed for a reduction of the spike-wave index. Intravenous methylprednisolone (solely pulse therapy was applied in 49% of centers), and oral prednisolone were the most commonly used steroids formulations, but other steroids used too. The majority of centers (80%) reported to always follow the same scheme, but the interindividual variability of schemes between centers was large.

**Conclusion:** The vast majority of European pediatric epileptologist use steroids as first line therapy in epilepsy with ESES. The formulations, dosages, and regimens used vary significantly. In addition, the inconsistent definition of ESES used and large variety between patients complicate assessment of efficacy of different schemes applied.

430 The role of the status epilepticus cessation in predicting 30-day mortality

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**Purpose:** The Status Epilepticus Severity Score (STESS) is accurate and effective in identifying patients with 30-day survival (high negative predictive value). Its predictive value for 30-day mortality is lower and needs to be further implemented. We investigated whether including SE cessation improves the predictive value of STESS.

**Method:** We included consecutive patients with SE admitted from 2013 to 2021 at Modena academic hospital. Through reclassification improvement analysis, we evaluated whether adding SE cessation to other STESS variables could improve the predictive capacity of this score. The outcome was 30-day mortality. Net reclassification improvement (NRI) was used to quantify the accuracy of the model adding the SE cessation to the STESS in reclassifying the risk of mortality compared to STESS alone. Furthermore, the net clinical benefit of adding the cessation of status epilepticus to the STESS was assessed with the decision curve analysis (DCA).

**Results:** Of the 711 included patients, 28.1% (200/711) died within 30 days from the SE. Compared to STESS variables alone, the inclusion of SE cessation improved the capability of this score in predicting 30-day mortality by a NRI index of 28% (SD 0.057, p <0.001). In patients who died within 30 days, the SE cessation increased the predictive capacity of STESS. The benefit was highest in the low-medium risk group (15-25%), with a net improvement in categorization of 46.6% (34/73) for patients who died at 30 days and 11.6% (29/249) for surviving patients. The DCA confirms that the model with the SE cessation added to the STESS leads to a net clinical benefit for wide thresholds of risk.

**Conclusions:** Adding SE cessation to STESS variables further increases its effectiveness in identifying patients with 30-day mortality.
Focal nonconvulsive status epilepticus with impairment of consciousness in the elderly: the relationship between prognosis and initial clinical EEG data and after an initial pharmacological protocol

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**Objective:** To evaluate the initial clinical-EEG data and after an immediate pharmacological treatment related to a 30-day prognosis of elderly individuals with focal non-convulsive SE with impairment of consciousness (NCSE-focal).

**Methodology:** Clinical-EEG data at diagnosis and after an initial pharmacological protocol were related, according to the 30-day prognosis of 45 elderly individuals with focal NCSE, with a significance level of \( p < 0.05 \).

**Results:** The mean age was 73.5±9.1 years. At the time of diagnosis, they all were confused/mentally downgraded and 24(20%) of them had stereotyped automatisms. In the EEG, lateralized periodic discharges (LPDs) and rhythmic delta activity (RDA) occurred in 25 cases, and electroclinical status epilepticus (ECSE) in 32 cases. After the drug protocol, there was clinical improvement in 33(73.3%) cases, maintenance of LPDs in 8 cases, RDA in 14 cases, and ECSE in 14 cases. A total of 10(22.2%) individuals died after 30 days of diagnosis. In the simple and multiple logistic regression, elderly individuals with ECSE and without LPDs in the initial EEG had a greater chance of clinical improvement (OR:9.00; CI(95%):1.08-97.10; \( p = 0.047 \)). In the simple regression analysis, a higher chance of death was associated with the presence of RDA at the time of diagnosis with its subsequent disappearance on the EEG (OR:6.93; CI(95%):1.20-46.01; \( p = 0.033 \)). The presence of LPDs after treatment was associated with a higher occurrence of death, in single and multiple regression analysis (OR:8.75; CI(95%):1.49-73.29;\( p = 0.023 \)).

**Conclusion:** In elderly individuals with NCSE-focal the occurrence of stereotyped automatisms as an initial manifestation was not associated with mortality. Clinical improvement at 30 days was associated with the presence of ECSE and the absence of LPDs on the EEG at the initial assessment. The presence of RDA and LPDs in the initial EEG and the maintenance of LPDs after initial treatment was associated with a higher occurrence of death.

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De novo non-convulsive status epilepticus (NCSE) in hospitalized patients with COVID-19

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**Purpose:** SARS-CoV-2 infection and its association with neurologic complications are well documented. Seizures in the setting of acute Covid-19 can include either relapse of AED controlled convulsions or de novo seizures, without any prior history. The result can either be isolated seizures or convulsive or non-convulsive status epilepticus. Hereby we present three cases of hospitalized patients with Covid-19 with NCSE and tried to establish the correlation between the dynamics of inflammatory markers (C - Reactive Protein, Interleukin - 6), overall clinical severity of COVID-19, and NCSE.

**Methods:** We collected data from the Central University Clinic After Acad. N.kipshidze, hospital severely affected by COVID pandemics. Collected data were assessed retrospectively. Each of these patients was diagnosed with NCSE, based on the Salzburg electroencephalographic criteria.

**Results:** In described instances, clinical suspicion was elicited by changes in mental and cognitive status. Each of these patients exhibited confusion, with variable impairment in memory and language. Prolonged EEG monitoring was performed which revealed, generalized polyspike and wave activity at 4 Hz. After intravenous midazolam, EEG showed resolution of epileptiform activity. Head MRI did not reveal any pathology nor did examination show focal neurologic abnormality. The analysis of serum inflammatory markers showed a progressive increase in quantity from the first day of admission, but an exact correlation could not be established. In each of these instances, clinical severity was assessed to be severe (according to the WHO definitions).

**Conclusion:** Consequently, it must be emphasized that great attention must be taken upon examining and assessing patients with possible NCSE. Sometimes the diagnosis of NCSE is delayed especially in critically ill patients with comorbidities, which may obscure the timely diagnosis, hence underling the crucial role of EEG monitoring in intensive care units.
Successful immunotherapy for status epileptics of a case with high titer of anti-glutamic acid decarboxylase antibodies

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Purpose: To investigate clinical features of status epilepticus of a patient with high titer of anti-glutamic acid decarboxylase (GAD) autoantibodies.

Methods: A 64-year-old female patient, who presented with drowsiness, recurrent loss of consciousness, restless sensation, and apathy (Day 1), was investigated. She had a 23-year history of type I diabetes. On admission, her GAD antibody titer was 2,270 U/mL in serum and 64.6 U/mL in cerebrospinal fluid (GAD index 0.82). She was negative for antibodies to cell surface neuronal antigens including NMDA, AMPA, GABAb, and glycine receptors, and CASPR2 and LGI1. Her clinical course, laboratory findings, and therapeutic responses were serially analyzed.

Results: Her mental state deteriorated over a week. In the next 2 months, she became unresponsive to verbal commands and akinetic with muscle rigidity. Then, right eye deviation and oral dyskinesia appeared. Her EEG on Day 62 showed rhythmic delta activities regional bilateral frontal areas and sharp waves in the left hemisphere. Treatment with lacosamide, levetiracetam and perampanel, based on the diagnosis of nonconvulsive status epilepticus, showed only limited effect. Combination of immunotherapy with intravenous methylprednisolone (1,000 mg/day, Day 57-59), plasma exchange (Day 72, 76, 79, 82), and intravenous immunoglobulin (0.4 g/kg/day, Day 96-100) was remarkably effective and she recovered to speak fluently. EEG on Day 96 improved with residual sharp waves restricted to the left parietal area. However, her memory disturbance and irritability persisted. On Day 186, GAD index was elevated to 2.89. MRI FLAIR images on Day 188 showed high-intensity lesions in the periventricular white matter of the left parietal lobe. Additional treatment with intravenous methylprednisolone (Day 186-189 and Day 201-203) improved her mental state, MRI lesions, and EEG findings.

Conclusion: Autoimmune encephalitis and status epilepticus associated with GAD antibody is one of the most refractory conditions, but can be treatable with intensive immunotherapy.

Status epilepticus caused by change in lifestyle rhythm

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Purpose: To explore factors to develop status epilepticus associated with change in lifestyle rhythm.

Method: A 31-year-old female who emerged with cluster of seizures lasting 8 hours was investigated. She worked from evening to midnight and regularly slept from daybreak to noon. For previous three days, she stayed at her parents’ house and changed her life rhythm to be a morning person. Sleep duration was kept constant. Her clinical characteristics were analyzed.

Results: Thorough history taking revealed that she had frequent urinary incontinence from 4-year-old, developed her first convulsion at age 16, had daily seizures around 26-year-old, and recently had monthly seizures. Video-EEG in the previous epilepsy center showed multiple seizure onset zones therefore epilepsy surgery was not indicated. Her seizure types were focal aware seizures of psychic feelings with sudden tachycardia, focal impaired awareness seizures of brisk clonic convulsion of both upper limbs with convergence gaze, holding her knees to her chest, violent movement and vocalization with urinary incontinence, and focal to bilateral tonic-clonic seizures. Her antiepileptic medications were carbamazepine 900 mg/day, levetiracetam 1500 mg/day, and diazepam suppository 10 mg as necessary. She was also taking analgesics, sedatives, and herbal medicines. Laboratory tests showed increase of white blood cells and creatinine kinase in blood, and elevation of IgG index in cerebrospinal fluid. Brain imaging was unremarkable. Status epilepticus was successfully suppressed using anesthetics. Afterward, she has been stable with monthly seizures exclusively associated with sleep for more than 5 years. Current medications are carbamazepine 900 mg/day, topiramate 250 mg/day, lacosamide 300 mg/day, and loxoprofen 60 mg according to need.

Conclusion: In sleep-related epilepsy syndromes manifesting with autonomic symptoms, not only sleep deprivation but also change in lifestyle rhythm can cause status epilepticus. Adult patients at night shift work should be cautioned about the importance of maintaining life rhythm.
Clinical features and outcome of status epilepticus in the elderly: data from the population of Modena, northern Italy

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Purpose: Status Epilepticus (SE) is a neurologic emergency with high mortality and morbidity rates. In line with the rising life expectancy, SE incidence in elderly patients is significantly increasing too. However, due to the lack of cohesive reports, elettroclinical features of SE in this population have not been well established yet.

Method: We reviewed our register of consecutive SE episodes occurred from September 1st 2013 to September 1st 2021. Post-anoxic episodes were escluded, while, for patients with more than one SE, only data of the first status were considered. We evaluated the differential characteristics of SE in elderly (≥ 65 years; eSE) compared to youger adults (18 – 64 years; ySE). Older patients were further classified as early-eSE (65 – 74 years), late-eSE (75 – 84 years) and very late-eSE (≥ 85 years) and compared to each other.

Results: 557 patients were included (mean age: 70 years). 392 patients were older than 65 years (71 %). An antecedent epilepsy was more common in younger adults than in older ones (40% vs 25%; p=0.001). Cerebrovascular diseases (141/392; 35%) and brain tumors (43/392; 11%) were the most frequent etiologies in eSE. Non convulsive SE (NCSE) occured more frequently in elderly patients (56% vs 40%; p=0.001). Despite no significant differences in treatment refractoriness between ySE and eSE (p=0.50), 30-day mortality was significantly higher in the elder population (7% vs 32%; p<0.001) and increased up to 52% in very late-eSE patients, in an age-dependent manner (p=0.002).

Conclusion: SE represents a frequent entity in elderly patients, especially in the setting of cerebrovascular diseases. In this population, SE diagnosis may be complicated and delayed by subtle non-motor clinical presentation. Even if an advanced age did not influence treatment response, SE in older patients were associated with a worse short-term outcome in an age-dependent manner.

Clonazepam in status epilepticus: dosage and its correlation with outcome

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Purpose: Benzodiazepines are the first treatment line in status epilepticus (SE). Despite their well-established benefit, benzodiazepines are frequently used underdosed with potential detrimental consequences. In Europe, clonazepam is most commonly used as the first line treatment. The aim of this study is to explore the correlation between CLZ loading doses and SE outcome.

Methods: Retrospective analysis of a prospective registry in Lausanne, Switzerland (CHUV Lausanne University Hospital), including all SE episodes treated between February 2016 and February 2021. Patient characteristics, SE features, a validated SE severity score (STESS) and treatment characteristics were prospectively recorded. We considered that loading doses of 0.015mg/kg or more were following previously published guidelines. We analyzed outcome in term of mortality, intubation for SE treatment, intubation for airways protection, number of treatment line after the CLZ, proportion of refractory episodes.

Results: We collected 287 SE episodes. In the total cohort, median CLZ loading dose was 0.1 mg/kg. Treatment Guidelines were followed in 21.9% of SE episodes. Thirteen percent of SE were intubated for airways control while 12.7% for status epilepticus treatment. Followed treatment guidelines were only independently associated with older age (68 yo vs 62 yo, p=0.002) and more frequent intubation for airways protection (23% vs 11%, p= 0.013). In term of mortality, only STESS (p<0.0001) and potentially fatal etiology (p< 0.002) were independently associated with death as outcome.

Conclusion: CLZ treatment guidelines in SE were more frequently followed in younger patients and led more often to the need of intubation for airways protection. CLZ dosage did not alter mortality in SE. Following treatment guidelines seems not to be a major determinant in SE outcome. Our results suggest that CLZ dosage in SE may be individualized depending the clinical setting.
**Comparative analysis of long-term seizure outcome in New-onset refractory status epilepticus (NORSE) patients: anti-NMDAR encephalitis versus cryptogenic NORSE**

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**Purpose:** Previous studies revealed that autoimmune or paraneoplastic encephalitis as specific etiologies of NORSE. However, about 50% of cases remained cryptogenic after extensive evaluation. Although patients experienced the same SE and were treated with similar immunotherapy, long-term seizure outcomes depend on the specific etiology of NORSE. Therefore, we studied and compared long-term seizure outcomes of cryptogenic NORSE and NORSE in anti-NMDAR encephalitis.

**Methods:** We retrospectively reviewed Seoul National University Hospital Autoimmune Encephalitis Registry. We included patients who were diagnosed with definite or possible autoimmune encephalitis (AE) whose initial presentation was SE. To obtain long-term clinical outcome and seizure outcome, patients with short follow-up period (<2 years) were excluded. In the registry, 17 NORSE patients of possible AE with no identified etiology after extensive work-up, were classified as cryptogenic NORSE. 19 anti-NMDAR encephalitis patients with NORSE presentation were also included. We compared seizure outcome, EEG findings, MRI findings and number of antiepileptic drugs (AEDs) between two groups.

**Results:** Compared to anti-NMDAR encephalitis cryptogenic NORSE patients had longer duration of SE days (34.88±11.38 vs. 16.76±13.15, \(P<0.001\)). In the initial EEG findings, cryptogenic NORSE patient mostly showed periodic epileptiform discharges (70.95%) while most of anti-NMDAR encephalitis showed rhythmic delta activities (78.95%). In Kaplan-meier survival graph for 3-months seizure free event, anti-NMDAR encephalitis showed significant superior outcome compared to cryptogenic NORSE (\(P<0.001\)). In anti-NMDAR encephalitis, about 50% of patients got 3-months seizure free between 6 to 9 months from disease onset. Long-term AED free rates were significantly higher in anti-NMDAR encephalitis (15/19 vs. 1/17, \(P<0.001\)).

**Conclusion:** Although initial presentations of SE were similar, EEG findings and long-term seizure outcome of NORSE were different according to specific etiology. It is assumed that the effect of epileptogenesis differs depending on the detailed etiology of NORSE. Further research on epileptogenesis in NORSE is required.

**Terminology and Classification**

**Exploring the feasibility of an interactive virtual avatar and automated conversation analysis in the differentiation of epileptic and dissociative seizures**

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**Purpose:** Linguistic and interactional observations in doctor-patient seizure consultations have been shown to assist the differential diagnosis of epilepsy and dissociative seizures. However, the expertise required to conduct close interactional and linguistic examination of communication is unlikely to be present in the emergency and primary care settings where people first present after a seizure. Our research explores whether observations previously made in face-to-face interactions between patients and doctors are still present in interactions between people who have experienced seizures and an interactive virtual avatar (IVA). Their documentation would raise the prospect of such observations being detected automatically and thereby contributing to an automated diagnostic procedure involving speech recognition and a decision-making paradigm.

**Method:** 21 people with diagnoses of epilepsy or dissociative seizures interacted with a computer-presented IVA who asked participants about their most recent seizure. Responses were recorded using patients’ mobile device or the computer which patients were using for the interaction with the internet-based IVA. In this proof-of-principle analysis, we used the qualitative methodology of conversation analysis manually to explore patients’ responses to the IVA and to observe whether the linguistic and interactional differences previously proven to support the differential diagnosis are still identifiable in this context.

**Results:** Although there are differences in how people speak to the IVA compared to a doctor, we found that the previously described linguistic and interactional differences of differential diagnostic value are still present in these interactions. However, some of the observations present differently in interactions with the IVA than in doctor-patient interactions.

**Conclusion:** These findings suggest that it may be feasible for a computer to automatically detect these linguistic differences.
Cerebral vascular malformations characteristics – retrospective study

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Purpose: Cerebral vascular malformations (CVM) represent a group of diverse vascular abnormalities which may cause a wide range of neurological symptoms or which can be incidentally discovered in routine brain MRI. The aim of our study was to characterize patients with CVM, especially in relation to the incidence and management of epilepsy in this group.

Method: We retrospectively reviewed medical records of 50 patients (including 30 women) who were hospitalized at the Department of Neurology or seen in our outpatient clinic. The following data were collected: demographics, CVM subtype and location, incidence of focal neurological signs and hemorrhages, treatment modalities, epilepsy diagnosis, antiepileptic drugs, and seizure outcome.

Results: 38 patients (17 females, 44.7%) were included in the analysis. Median age was 38.5 (quartiles: 30-48). Cavernous malformations (CM) were detected in 25 (65.8%) patients, arteriovenous malformations (AVM) in 12 (31.6%) and developmental venous anomalies (DVA) –1 (2.6%). Most common localizations of CVM were temporal lobe (11, 28.9%) and frontal lobe (9, 23.7%). Focal signs were present in 10 (26.3%) and a quarter of patients (11, 28.9%) suffered from brain hemorrhage in the past.

Epilepsy has been diagnosed in 33 cases (84.2%), mostly used antiepileptic drugs were valproic acid (11, 28.9%) and levetiracetam (9, 23.7%). 18 (47.4%) patients were seizure-free.

Conclusion: Epilepsy is a common diagnosis among patients with cerebral vascular malformations and in majority of patients remission can be achieved.

Epilepsy and the translation of Epilepsy Monitoring Unit events into accurate clinical diagnosis

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Purpose: The aim of this audit was to review the initial clinical assessment of patients in Beaumont Hospital’s Epilepsy Monitoring Unit (‘the EMU’) and to determine if patients’ seizures were being appropriately classified. A particular concern was that subjective events recorded in the EMU were being translated into ‘non-epileptic events’. This could be understood by some less experienced staff to mean ‘psychogenic non-epileptic events’.

Method: The baseline audit was a retrospective review of 20 patients who were admitted to the EMU between November 2019 and January 2020. There was a retrospective re-audit of a further 49 patients admitted between May 2020 and August 2020. These patients were admitted for either diagnostic reasons or pre-surgical evaluation. Patient electronic records, telemetry EEG, discharge letters, and any attached documents, such as MRI reports, were reviewed. Pre-admission diagnosis was considered while reviewing the final diagnosis in the discharge letter.

Results: In the baseline audit of 20 patients, 11 had clear communication of diagnoses, 8 had minor or medium errors, and there was 1 significant miscommunication of epilepsy diagnosis. Errors included inaccurate recording of patient details, incorrect or incomplete communication of EEG findings, and poorly-worded test results. Of the 49 patient re-audit files reviewed, 42 patients had a clear and accurate diagnosis and 6 files had minor errors. 1 file could not be located.

Conclusion: This review highlighted the importance of maintaining accurate patient records and classifying and communicating accurate diagnoses using the current International League Against Epilepsy (ILAE) framework. A standardised protocol for categorising errors, combined with continued regular reviews, will help transform these errors into learning opportunities for future patient engagement. There was a significant reduction in error rate between the initial audit and the re-audit, showing the benefits that can be gained from discussing and learning from these reviews.