P1 A Child with Refractory Autosomal Dominant Nocturnal Frontal Lobe Epilepsy Treated with Transdermal Nicotine

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Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) was identified as a distinctive clinical syndrome by Scheffer et al. in 1995. It is characterized by clusters of nocturnal motor seizures, which are often stereotype and brief (seconds to a few minutes). They vary from simple arousals from NREM sleep to dramatic, often bizarre, hyperkinetic events with tonic or dystonic features. Retained awareness during seizures is common. Onset ranges from infancy to adulthood, mean age of onset is ten years. Molecular genetic testing reveals pathogenic variants in CHRNA4, CHRNB2, CHRNA2, KCNT1, DEPDC5, or CRH in approximately 20% of individuals with a positive family history.

The patient presented, at five years of age, short, up to 30 nocturnal episodes of arousal and uncoordinated, sometimes violent, movements in arms and legs. Increased daytime sleepiness, anxiety and attention difficulties was also recognized. Both parents had epilepsy and became seizure-free in young adulthood. Both were smokers as young adults. Focal epilepsy with hyperkinetic seizures and preserved awareness was confirmed with video-EEG and several anti-epileptic drugs failed to provide benefit. Genetic testing showed the presence of a serine 284 to leucine mutation in the CHRNB2 gene, c.859G>A; p.V287M (het.) in exon 5, NM_000748.2, rs74315291:.

Since the epilepsy was treatment-resistant with anti-epileptic drugs and epilepsy surgery was not indicated, alternative treatments, including ketogenic diet and vagal nerve stimulation (VNS), were discussed. Despite her young age, but according to the genetic testing with a mutation in a gene coding for a neuronal nicotinic acetylcholine receptor indicating a defect cholinergic neurotransmission, a seven mg nicotine patch was applied to her skin two hours before bedtime and was removed in the morning. A prompt resolution of all clinical events was seen from day one and improvement of sleep, daytime sleepiness, anxiety and attention difficulties was noticed. After two weeks, treatment was stopped, and four days later seizures returned. The nicotine patch was reintroduced, again with prompt resolution of seizures. Dizziness and nausea were noted but disappeared with a dose reduction to 1,75 mg nicotine. At three months follow-up a v-EEG during 48 hours was performed with no clinical or electrographic seizures.

We present a case of treatment-refractory ADNFLE responding to a low dose of transdermal nicotine treatment. From the first day of treatment there was a complete resolution of epileptic seizures and a dramatic improvement of sleep and behavior. There are a few case-reports on the relationship between ADNFLE and nicotine-treatment. This is, to our knowledge, the first report of a child. Thus, the disruptive effect on quality of life of uncontrolled nocturnal seizures, day-time sleepiness and anxiety must be weighed against the potential chronic long-term side effects of nicotine for each individual. There are, however, limited data on the long-term safety of intermittent nocturnal low-dose treatment and efficacy of this treatment, especially regarding children.

P2 Correlation of hydrocephalus, shunt therapy, and epilepsy in infancy and childhood

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Epilepsy is a major comorbidity in children with hydrocephalus (HC) and has a serious impact on outcome. There are variable influencing factors, and the individual risk for developing epilepsy remains still unclear. Cortical damage due to increased intracranial pressure, shunt insertion, shunt revisions as well as complications and etiology of HC are thought to be related to the risk of epilepsy. Our aim was to quantify and analyse the risk and risk factors for developing epilepsy in infants and children with shunted hydrocephalus.

We retrospectively analysed 371 patients with the diagnosis hydrocephalus treated at the university children´s hospital Frankfurt from 2004 to 2017. The following factors were considered: age at HC diagnosis, time to shunt-treatment and number of revisions, shunt complications, development of epilepsy, epilepsy course well as the etiology of HC. The data were first summarized descriptively. The influence of the occurrence of HC was analysed by means of a Cox regression. Subsequently shunt therapy (including revisions) on the development of epilepsy was investigated. The mentioned risk factors were included in the analysis as time-dependent variables.

The most common cause of hydrocephalus was cerebral haemorrhage (n=123). The median age at development of hydrocephalus was 15 days. 305 of 371 children had a ventriculo-peritoneal shunt implantation. 147 of 371 children with HC developed epilepsy (39.6%) and 129 of 305 shunt- treated children (42.3%). 19 children with HC developed epilepsy without shunt implantation (28.8%). The median age at the first manifestation of epilepsy was 300 days. The probability for developing epilepsy after HC was decreasing with increasing age. 42 of 128 children developed pre-shunt epilepsy (32.8%), 86 children post-shunt epilepsy (67.2%). Within a mean duration of thousand days after diagnosis of HC, 30% of the children had a diagnosis of epilepsy.The HC itself (hazard ratio (HR) 5.5; 95% confidence intervals (95% CI) [3; 9.8]; p-value 1.73e-8) shows the greatest significant influence on the development of epilepsy.Hydrocephalus caused by brain haemorrhage is associated with the highest risk for developing epilepsy (HR 7.4; 95%-CI [3.9; 13.95]; p<0.01). Shunt insertion has a lower influence (HR 1.7; 95%-CI [1; 2.6]; p= 0.026). The probability of developing epilepsy increases stepwise per shunt revision, up to HR 2.19; 95%-CI [0.82; 5.85]; p= 0.12 after 5 revisions.Shunt implantation at a younger age (<30; <200 days) has no significant influence on the development of epilepsy (<30 days: p >0.2; <200 days: p=0.14), nor does sex (p >0.2).

The development of epilepsy is mainly correlated to the underlying etiology of the hydrocephalus. The greatest risk factor for the development of epilepsy seems to be brain haemorrhage (as the cause of HC). The shunt implantation itself seems to have a smaller influence on the development of epilepsy, likewise the number of revisions. In this study, age at shunt treatment and sex appear to have no influence on the development of epilepsy.

P3 Refractory spasms of focal onset- A potentially curable disease thatshould lead to rapid surgical evaluation

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Infantile spasms (IS) can occur as the only seizure type in children with surgically amenable epilepsies. Although early surgery has shown positive effects, little is known regarding outcomes.

We retrospectively reviewed all children with IS referred to our tertiary center between 2002 and 2014 and try to define factors of outcome.

Sixty-eight children with focal onset were referred: twenty children with a hemispheric implication and 48 with one or more lobes involved. The age of onset was significantly earlier in the hemispheric population (8.0 versus 16.7 months in the focal population). There was no difference in the age of onset between anterior and posterior onset zones, as we could expect regarding the maturation gradient. The epilepsy began earlier in life in tuberous sclerosis than in DNET. Only 3 children of the 48 non-hemispheric patients had a normal MRI at the time of the surgery. Temporal lobe was involved only in a third of the population. More than 86% of the patients were operated on. Patients with hemispheric lesions were operated on younger (2.6 years +/- 2.1 years) compared to 4.6 +/- 3.5 years in the whole population. The most frequent etiologies were in descending order: dysplasia, ganglioglioma or dysembryoplastic tumours and tuberous sclerosis. The global seizure outcome was favorable (Engel 1a) in 74.6% of the patients, and 87.9% if the delay between the first seizure and the surgery was less than 36 months. It fell to 64.7% if the delay exceeded 50 months.

Focal spasms have a similar postsurgical outcome as other seizure types so surgery may be an excellent option for treating selected patients with focal infantile spasms. Volume and type but not topography of the lesion influence the age of onset. MRI is very helpful to locate the pathology in the pediatric population, since only a small portion had a normal MRI.

P 4 Epileptic opsoclonus due to cortical dysplasia of the inferior parietal lobule in a child: An ocular EEG study

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Opsoclonus has been associated with seizure activity but the implications for epileptogenic zone localization are not fully understood. Opsoclonus with or without other oculomotor features has been observed infrequently in patients with posterior cortex epilepsy (PCE). Kahane et al. (2003) stimulated vestibular cortex in 260 patients with parietal lobe epilepsy and identified oscillopsia associated with a sensation of falling flat in one patient during stimulation of the right precuneus (BA7, 50 Hz, 1 mA), but neurophysiological confirmation was not possible due to absence of ocular electrodes during the invasive evaluation. Here, we describe a case of epileptic oculogyric events evaluated using ocular EEG electrodes and simultaneous video recording.

A 7-year-old right-handed girl presented with recurring episodes of a spinning feeling “like a ceiling fan” with no perceived direction of rotation, occurring 10-20 times per day, each episode lasting for 15-20 seconds. No body movements were observed, but immediately following this sensation, her parents reported “funny eye movements” while she remained unresponsive to questions. There was no seizure risk factor and no recent illness with fever.

A 3-Tesla brain MRI, lumbar puncture, and routine blood tests were normal. Four antiepileptic drugs (AED) and a 4-day steroid course did not alter her symptoms. A video EEG study showed: Sharp waves in the left parietal region, shifting maximum negativity over electrodes P3/P7/T7. Continuous slowing in the left posterior quadrant. Multiple seizures that begin with her complaint of “spinning feeling,” followed by continuous, multidirectional, conjugate movements of both eyes, sometimes associated with unilateral or bilateral upper eyelid clonus. EEG seizures localized to left P7. She was unresponsive to questions during seizures. International 10/10 EEG system further localized the left parietal sharp waves to CP5/P5 with seizure onset at CP5, P5, P3, and P7. Video recording including electrooculogram and submandibular montage (Rosado et al. 2018) confirmed the presence of opsoclonic seizures. FDG-PET scan demonstrated hypometabolism in the left inferior parietal area. Neuropsychological assessment revealed average intellectual abilities and no significant lateralizing or localizing signs. The interictal and ictal EEG findings, seizure semiology, and FDG-PET indicated a likely left partietal epileptogenic zone. Invasive evaluation using a 64-contact subdural grid recorded numerous spontaneous, typical seizures localized to the P7. Electrical stimulation of the grid electrodes did not induce opsoclonus, eyelid clonus, or vertiginous sensations. The patient underwent a tailored resection of the inferior parietal lobule with resolution of epileptiform discharges on intraoperative corticography. Histopathological analysis identified ILAE Type 1 focal cortical dysplasia. Postoperative 48-hour video EEG at 6 months showed only focal slowing over the left parietal region, and she remains seizure free on oxcarbazepine 14 months after surgery.

Our findings support the concept that the sympotomatogenic zone of epileptic “oscillopsia,” “oculogyria,” or “opsoclonus” is associated with the posterior parietal cortex, consistent with prior studies describing oscillopsia during electrical stimulation of the right precuneus. Recording and stimulation using intracerebral electrodes with simultaneous video recording and electrooculogram may provide additional insight into this phenomenon.

P5 Hemispherotomy: a single-institution experience with special emphasis on outcomes and complications.

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Hemispherotomy is recognized as an effective and safe option for surgical treatment of patients with intractable epilepsy and unilateral hemispheric brain lesions. We present a single-institution experience of using this procedure in a pediatric cohort. The study aim is to assess and highlight variables affecting the outcome and morbidity.

We retrospectively reviewed the medical data, including medical records, imaging, and EEG for 79 children, aged 4 months through 17 years (median age - 4 years), who underwent hemispherotomy from 2006 through 2018. All data were extracted from the institutional epilepsy surgery database. All patients harbored a unilateral hemispheric lesion and presented with multiple DR-seizures (focal and/or focal with bilateral generalized T-C). Some patients were already hemiparetic at surgery, others showed various degree of developmental decline. An acquired pathology had been diagnosed in 35 patients, most often a sequence of perinatal stroke (33 cases). Rasmussen encephalitis (9 cases) and Sturge-Weber disease (5 cases) comprise the group with “progressive” etiologies. In the remaining 30 patients, the anatomical substrate of epilepsy was developmental in origin: widespread multiple lobe cortical dysplasia (24 cases), hemimegalencephaly (4 patients), and tuberous sclerosis complex (2 cases). Forty-three patients had left-sided lesions; the right hemisphere was affected in the remaining 36 cases. Two different techniques were used to isolate the epileptic hemisphere: the lateral periinsular (43 patients) and the vertical parasagittal (36 patients). Two patients required follow-up surgery to complete dissection of undercut commissural fibers, due to relapse and persisting seizures.

Various complications were noted in 16 cases (20%): severe and life-threatening deterioration and/or unanticipated new and permanent neurological deficit – in 5 (one of them died on the 5th day post-op (1,3%)); less disabling and temporary dysfunction (most frequently dysphagia) – in 5 other patients (6%). Hydrocephalus and shunt requirement were noted in 3 cases (4%) within 1,5 to 7,5 months post-surgery. Catamnesis for more than 6 months is known in 51 children (range: 6 months – 4,5 years; med – 2 years). Forty of them are free of seizures (78,5%) and AE-drug treatment was discontinued or tapered in 37 cases (73%). However not proven statistically, the etiology of epilepsy and its history (length of duration) showed some relation to outcome: e.g., those with acquired conditions generally do better, particularly if operated on early in the course of their epilepsy. A learning curve also exists, with experience gained in terms of both morbidity and achievement of SF-status. There were no evident differences among two hemispherotomy techniques, either in terms of loss of blood or length of stay in ICU. However, the vertical parasagittal technique looked quite feasible in almost every case, including complex hemimegalic brains with narrowed and distorted ventricles.

Hemispherotomy is an effective procedure to treat intractable structural hemispheric epilepsy. Achievement of SF-status requires complete disconnection of the hemisphere and the choice of technique depends upon a given patient’s individual anatomy and the surgeon’s experience. However, the etiology of epilepsy has also some link to

final outcome, with patients who have acquired pathologies seeing better chances compared to those with developmental etiology.

P6 Epilepsy patients with TSC1 and TSC2 gene mutation :clinical and scalp EEG feature analysis

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Tuberous sclerosis is a multisystem disease caused by TSC1 and TSC2 genes. The purpose of our study was to analyze the gene mutation in 24 patients with tuberous sclerosis with epilepsy as the main clinical manifestation, and to clarify the diagnosis. The genotypes of Chinese patients with tuberous sclerosis were analyzed. The relationship between genotype, clinical phenotype and scalp electroencephalogram in patients with tuberous sclerosis was analyzed.Tuberous sclerosis is a multisystem disease caused by TSC1 and TSC2 genes. The purpose of our study was to analyze the gene mutation in 24 patients with tuberous sclerosis with epilepsy as the main clinical manifestation, and to clarify the diagnosis. The genotypes of Chinese patients with tuberous sclerosis were analyzed. The relationship between genotype, clinical phenotype and scalp electroencephalogram in patients with tuberous sclerosis was analyzed.

Peripheral blood was extracted from all patients and their families, and TSC1 and TSC2 genes were tested by second-generation sequencing, to identify the gene mutation sites and types. All patients were monitored by scalp long-range video electroencephalogram (EEG) to determine the onset area and pattern of epilepsy.

A total of 19 patients had TSC gene mutation, including 7 patients with TSC1 gene mutation and 12 patients with TSC2 gene mutation. Fourteen of the mutations were spontaneous. Among all the mutation types, 3 are missense mutations, 6 are frame-shift mutations, 2 are splicing mutations, 5 are nonsense mutations, 2 are amino acid deletions, and 1 is large fragment deletion. In this paper, 7 unreported mutation loci were found, accounting for 36.8%. The clinical manifestations of patients with TSC2 gene mutation were more severe than those with TSC1 gene mutation. There were a total of 9 patients with focal initiation of scalp EEG during the paroxysmal phase, among which 8 patients with TSC2 gene mutation had focal origin of scalp EEG, and 4 patients started from the frontal- central area. The type of onset before 1 year old was dominated by tonic seizure, while the type of epilepsy after 1 year old was dominated by hyperactivity and automatism.

This paper mainly studies the relationship between genotypes and clinical manifestations in Chinese patients with tuberous sclerosis. Relationship between genotype and scalp EEG. This study is of great significance for genetic counseling and prenatal diagnosis of children and their families, and is also of guiding significance for surgical evaluation of patients with tuberous sclerosis.

P7 Genetical pecularities of the epilepsy in multiplex families

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Genetic biomarkers and pharmacogenomics constitute an emerging field with a huge potential to influence our decisions for treatment of epilepsy in the future [Weber YG et al., 2014]. Early epilepsy gene discoveries used the strategy of ascertaining very large families, typically with 10 or more affected individuals, where the family history supported the presence of simple inheritance, and success utilizing parametric linkage analysis was likely [Thomas RH et al., 2014]. More recently, de novo mutagenesis has emerged as the major genetic mechanism in epileptic encephalopathies and rapid progress has been facilitated by whole exome sequencing [Epi4K Consortium et al., 2013; Euro Epinomics, 2014].

We performed a search of the medical literature by using Google Scholar, PubMed, ResearchGate and PMC databases. We searched for the terms “multiplex families with epilepsy”, “familial epilepsy inheritance”. And we selected all articles from the last 5 years (2014-2018). In addition, we reviewed the reference list from all identified articles to identify other papers related to the subject.

The epilepsy diathesis hypothesis suggested that a familial predisposition for epilepsy exists due to the inheritance of susceptibility variants. In support of this was the discovery that rare inherited copy number variants can increase risk for different epilepsy syndromes [Lal D et al., 2015]. Epidemiologic studies, including twin analyses, have shown the risk of epilepsy to be higher in the relatives of probands with generalized epilepsy than in the relatives of probands with focal epilepsy [Peljto AL et al., 2014]. In 2011, the International League Against Epilepsy (ILAE) launched the Consortium on Complex Epilepsies. In 2014, the first such meta-analysis was reported. This led to the identification of new epilepsy loci [ILAE Consortium on Complex Epilepsies, 2014]. In 2016, Afawi Z. et al published their results on 211 families ascertained over an 11-year period in Israel, and pathogenic variants were identified in 49 families (23%). The majority were found in established epilepsy genes, but in 11 families, this cohort contributed to the initial discovery [Afawi Z, 2016]. A recent analysis of exome sequencing in unrelated individuals with a family history of epilepsy shows an increased burden of ultra-rare variants among the currently known epilepsy genes [Epi4K Consortium et al., 2017]. In 2017, the Epi4K Consortium, assembled and analysed another cohort of 303 families. Their findings suggest that specific patterns of syndromic familial aggregation occur, including newly recognized forms of familial focal epilepsy. One-third of families with features of both focal and generalized epilepsy shared genetic determinants [Epi4K Consortium, 2017]. Single gene causes of the more common forms of epilepsy appear to be relatively rare [Epi4K Consortium, 2017]. They are likely to be multifactorial, with a significant and complex genetic architecture [Koeleman, BPC, 2018]. Recently, a Genome-wide mega-analysis identified new 16 epilepsy loci. Importantly, 11 of these loci are associated with the genetic generalized epilepsies; the group of epilepsies where despite having the highest heritability we have made the least genetic progress to date [International League Against Epilepsy Consortium on Complex Epilepsies, 2018].

Almost all previous studies of familial risk of epilepsy have had potentially serious methodological limitations, such as referral and reporting biases, small sample size, ambiguous disease definitions in probands and relatives, lack of controls, and failure to control adequately for age in the relatives. Improvement in genomic technologies and research methodology is expected to increase the chances of uncovering truly predictive genetic markers for epileptogenesis and further the advancement of epilepsy pharmacogenomics.

P8 Late Corpus Callosotomy In Patients With Lennox-Gastaut Syndrome Of Infancy Onset

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Lennox-Gastaut Syndrome (LGS) is a drug resistant encephalophathy with typical onset during infancy; in both developed and developing countries access to epilepsy surgery is delayed due to different variables (ref). Herein we describe postoperative EEG findings is a cohort of patients with LGS where callosotomy was not performed until adulthood. Few studies have described EEG findings pre and post corpus callosotomy in adult patients.

Observational cohort of 38 adult patients with LGS submitted to corpus callosotomy from 2005-2018. Patients' pre and postop EEGs had to be available and they were followed up for two years. A database was performed in SPSS. Descriptive analysis for for quantitative variables consisted on means and SD and percentages for qualitative variables. Univariate analysis was performed using chi X 2 or Fisher's exact test.

Twenty nine (76.3%) were open callosotomies and 9 (23.6%) were done by radiosurgery. A predominance of male patients was seen 26 (63.4%), age of onset of LGS was at 20 months, more than half of the patients had neonatal hypoxia (n=21/55%). Mean age at corpus callosotomy was 26±7 years old. In the analysis of the EEGs pre and postop, there was a significant improvement in the basal activity (92.1% vs 63.2% p= 0.001); pre-callosotomy EEG showed generalized activity that also became focal postop (2.6% vs 39.5% p= <0.001). Pre-op EEG was normal in one patient (2.6%) while four (10.5%) had a normal EEG post-op (p= 0.070). Mean overall seizures pre-callosotomy were 184 per month and post-callosotomy seizures were 52 (p= 0.002). Seizure frequency by type preop and postop was as follow: Tonic seizures (103.21 vs 2.13), atonic seizures (105.43 vs 2.65), GTCS (86.46 vs 3.71), myoclonic seizures (39 vs 2.6) and atypical absences (82 vs 5.55). According to the ILAE epilepsy surgery outcome scale: thirty-one patients (81.6%) had a third grade of impromevement and seven patients (18%) had a fourth grade. All these were statistically significant ($p < 0.05$).

There were significant changes in basal and epileptic activity regarding pre and postcallosotomy EEGs in patients with infancy onset LGS operated in adulthood. This improvement in the EEG might in some cases contribute to improve the encephalopathy and long-term cognition. Focalization of the epileptic activity might also help to perform a second surgery in some of the patients. Corpus callosotomy (either open or by radiosurgery) is a procedure traditionally considered as "palliative", however, it is an important therapeutic resource in developing countries, like Mexico. Nevertheless is performed late in adulhood. In spite of that, seizure improvent was seen in all patients. REFERENCES: Ladino LD, Benjumea-Cuartas V, Vargas-Osorio J et al. [Barriers impeding access to epilepsy surgery: a review of the literature]. Rev Neurol. 2017 Sep 16;65(6):268-279. Review. Spanish. Martínez-Juárez IE, Funes B, Moreno-Castellanos JC, et al. A comparison of waiting times for assessment and epilepsy surgery between a Canadian and a Mexican referral center. Epilepsia Open. 2017 Oct 19;2(4):453-458.

P9 Stereo-EEG seizure localization in patients with non-lesional MRI and unilateral temporal lobe hypometabolism on PET

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Epilepsy surgery is superior to medical therapy in refractory temporal lobe epilepsy; however, in many cases the decision algorithm for pre-operative evaluations is generally based on empirical and center-specific logistics. Patients with temporal lobe epilepsy and non-lesional MRI, but abnormal fluorodeoxyglucose-PET (FDG-PET) demonstrating unilateral temporal lobe hypometabolism may have good surgical outcomes after standard anterior temporal lobectomy without invasive evaluation before resection. Nevertheless, it is not clear how to identify patients in this cohort who might not benefit from a standard ipsilateral anterior temporal lobe resection.

We included all patients with ictal semiology and scalp EEG suggesting temporal lobe epilepsy, who had non-lesional brain MRI but FDG-PET demonstrating unilateral temporal lobe hypometabolism, and then underwent stereo-EEG (SEEG) evaluations at our institution. Patients with previous resective neurosurgeries were excluded. We analyzed PET and SEEG localization results.

Among 124 SEEG patients screened, 16 patients met inclusion and exclusion criteria. In this patient cohort, the SEEG localized seizure onset was concordant with the PET abnormality in 11/16 (69%) patients. Within this concordant group, only 6 had ipsilateral mesial temporal ictal onset; in 2 patients, SEEG ictal onset was ipsilateral neocortical temporal; and 3 had independent ipsilateral mesial temporal and ipsilateral neocortical temporal ictal onsets localized by SEEG. Among the 5/16 (31%) patients who had discordant FDG-PET and SEEG localization, 2 had contralateral mesial temporal ictal onsets, 1 had independent bilateral mesial temporal ictal onsets, 1 had ipsilateral neocortical temporal and ipsilateral extra-temporal ictal onsets, and 1 had ipsilateral extra-temporal (insula) ictal onset on SEEG relative to the FDG-PET hypometabolism.

Our study suggests that unilateral temporal FDG-PET hypometabolism in MRI non-lesional temporal lobe epilepsy frequently predicts an ipsilateral mesial and/or neocortical temporal epileptogenicity. Yet, the surgical decision should not be based solely made on FDG-PET data, since nearly 1/3 patients in our cohort actually were found to have discordant seizure onset by SEEG relative to the pre-operative FDG-PET. Thus, intracranial EEG evaluation in such patients may be necessary to fully evaluate the extent of epileptogenicity and inform surgical planning. Ultimately, larger studies are needed to replicate these findings and create guidelines for the role of invasive evaluation in MRI non-lesional temporal lobe epilepsy surgery candidates with unilateral FDG-PET temporal hypometabolism.

P10 Surgical treatments of epilepsy induced by tuberous sclerosis complex

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Tuberous sclerosis complex (TSC) is a disorder of aberrant neuronal differentiation and proliferation manifesting as multiple central nervous system hamartomas. Partial seizures are frequent, and although antiepileptic drugs may reduce the seizure frequency, medical therapy is not effective in many patients. Although most have multiple and bihemispheric tubers, their seizures often arise from a single tuber. This observation has important practical consequences because excisional surgery becomes a viable therapeutic option once a single epileptogenic tuber/region (ET/R) is identified.

A retrospective analysis was made of clinical semiology, and EEG features and imaging characteristics of 51 patients with epilepsy induced by tuberous sclerosis ,ages range from 6 months to 30 years old(mean 7.7 years), who received operations in the epilepsy center of Yuquan Hospital of Tsinghua University， from June 2007 to June 2018. We focused on how to identify epileptogenic tuber/region (ET/R), and the choice of different surgical procedures and the analysis of different prognosis.

24 patients receiced one stage resection, 11 patients receiced subdural electrode implantation for location of epileptogenic zone and then resection, 16 patients receiced stereotactic electroencephalography （SEEG） electrode implantation and then SEEG-guided thermocoguation were performed for epileptogenic tuber or region,if the outcomes were unsatisfied the operations of resecion were performed . All patients were followed up for 8 months to 11 years, According to Engel classification of epilepsy prognosis,40 of the 51 patients were Engel 1, 6 patients were Engle 2,5 patients were Engle 3.

Surgical resection of an epileptogenic tuber/region alleviates seizures in most patients with TSC and intractable epilepsy. The clinical semiology, EEG or/and intracraniol EEG and imaging characteristics help define the epileptogenic tuber/region and then we can choose the appropriate surgical procedure to control seizures.

P11 Surgical outcomes in patients with epilepsy after viral encephalitis: contribution of SEEG study

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Nowadays, few surgery analysis has been reported in cases of epilepsy after encephalitis. Herein, the purpose of this retrospective study was to evaluate the efficacy of surgery and capability of stereoelectroencephalography (SEEG) in the definition of the site and extension of the epileptogenic zone (EZ) after VE, and also to explore the relationship between the SEEG features and the surgical outcomes.

We retrospectively analyzed 10 surgically treated patients that identified to suffer from epilepsy secondary to VE using SEEG, and investigate the SEEG features associated with surgical outcomes of patients with epilepsy after VE. In addition to visual analysis, we also calculated the epileptogenicity index (EI), a quantitative and supplementary tool to evaluate the validity of SEEG in the context of VE.

Among the 10 operated patients, 3 of them became completely seizure-free. The patients who got totally seizure free or significant improvement, the seizure onset was located either in the antero-mesial temporal structures or focal gyrus; patients who got worthwhile improvement or no improvement, the seizure started from multiple brain lobes. The number of electrodes classified as epileptogenic visually involved were closely correlated with EI. Anatomic areas that was regarded as the seizure onset zone based upon the visual assessment were also defined as epileptogenic by the EI in these cases.

Apart from exploring the surgical outcome related to epilepsy after VE, we also bring insight into the relationship between the SEEG features and surgical outcome with the application of the supplementary methods.In our study, we found that patients who got totally seizure free or had significant improvement had restricted seizure onset located either in the antero-mesial temporal structures or focal gyrus with the application of SEEG technology, which makes the accurate localization possible. EI is a quantitative measurement method, which can be used as a potential supplement to the standard visual analysis of the SEEG data, and the validity of this technique is evaluated in the context of VE. EI values were high and restricted to confined area in those patients who got curative or palliative outcome.

P12 An Unusual Genetic Epilepsy Syndrome

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In this case report we are presenting a young girl child with severe drug refractory epilepsy. She had almost 100 attacks of seizures per day. On evaluation we found an unusual genetic cause for the same. We describe the treatment strategy employed which led to a complete control of seizures in her.

Baby T was referred to us at 2.5 years of age with recurrent seizures since 7 months of age. She had tonic and hemiclonic seizures involving upper limbs. She had developmental delay and regression of milestones since 1.5 years of age. She developed involuntary stereotypical movements involving both lower limbs and history of tantrums and hyperactivity. She was on multiple antiepileptic drugs with poor seizure control. On examination she was right handed and there were no lateralizing deficits. A provisional diagnosis of early onset epileptic encephalopathy was made and investigations were done. Electroencephalography revealed right frontocentral sharp transients in the background of diffuse slowing. Video EEG recording showed multiple hypermotor events of uncertain lateralization.Her routine blood investigations were normal .Tandem mass spectrometry results was normal. Her brain MRI revealed bilateral globus pallidus hyperintensity. Genetic analysis (targeted gene sequencing) showed a rare homozygous variation in CNTNAP2 gene and heterozygous variation in SCN2A gene. Ketogenic diet was initiated and the patient attained good seizure control and her development improved.

Contactin-associated protein-like 2 (CASPR2) is encoded by CNTNAP2 and clusters voltage-gated potassium channels (K v1.1) at the nodes of Ranvier. Intractable focal seizures begin in early childhood, after which language regression, hyperactivity, impulsive and aggressive behavior, and mental retardation develop in all children. Tissue abnormalities in brain specimens from patients with CNTNAP2 mutations were diffusely distributed throughout the hippocampus, amygdala, neocortex, and subcortex indicating that cerebral abnormalities of the syndrome could be widespread.Voltage-gated sodium channels, which consist of one major alpha-subunit and one or more beta-subunits, control the conduction of action potentials in the human brain. Nine types of alpha-subunits (Nav1.1–Nav1.9) have been identified. Among them, Nav1.2 is encoded by the SCN2A gene and is present mostly in the excitatory neurons during the early period of development. Mutations in the SCN2A were first identified in the families of patients with benign familial neonatal-infantile seizures (BFNIS); however, the mutation is now known to cover a wide spectrum of disorders ranging from autistic features without epilepsy to several types of epileptic encephalopathies, including Ohtahara syndrome (OS), Dravet syndrome (DS), and Epilepsy of infancy with migrating focal seizures (EIMFS).

Early Onset Epileptic Encephalopathy (EOEE) is a devastating neurological condition that causes progressive decline in cerebral functions. One third of EOEE cases are classified as cryptogenic where genetic factors are considered to play an important role. We highlight an unusual genetic cause for EOEE and the response to ketogenic diet in this case. References : 1. Early-onset epileptic encephalopathies and the diagnostic approach to underlying causes Su-Kyeong Hwang, MD, PhD, Soonhak Kwon, MD Korean J Pediatr 2015;58(11):407-414

P13 Brain somatic mutations in genes of the mTOR pathway cause epilepsy associated to malformations of cortical development

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Focal cortical dysplasia (FCD) and hemimegalencephaly (HME) are epileptogenic developmental malformations of the cerebral cortex characterized by dyslamination, enlarged dysmorphic neurons and balloon cells. Here we aimed to assess the role of brain somatic mutations in mTOR pathway genes in the pathology.

We collected in a monocentric study 80 children who underwent epilepsy surgery and received a neuropathological diagnosis of FCD or HME. We performed ultra-deep targeted capture sequencing of paired brain-blood samples to search for mosaic variants in mTOR genes, and phospho-S6 immunohistochemistry to assess mTOR activity.

We identified brain somatic activating missense variants in MTOR and its activators (AKT3, PIK3CA, RHEB) and loss-of-function variants in repressors of mTOR (DEPDC5, TSC1, TSC2), representing a diagnostic yield of 62% (37/59) of the FCD2 cases. Variant allele frequencies ranged from 0.3% to 18.6% in FCD and 7.5% to 34% in HME. In contrast, FCD1 cases were not related to mTOR signaling, and harbored SLC35A2 variants 20% of cases.

This study emphasizes that FCD type 2 are mTORopathies caused by brain mosaic variants arising during early stages of brain development, while FCD1 are not related to mTOR pathway, but rather to SLC35A2 variants.

P14 Potassium citrate supplementation to the ketogenic diet prevents metabolic acidosis in drug resistant epilepsy: a historical prospective controlled study

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The aim of the study was to investigate if potassium citrate can prevent metabolic acidosis in children treated with ketogenic diet for epilepsy, without reducing antiepileptic efficacy. Citrate is metabolized to bicarbonate in the liver and thus acts as a mild alkalizing compound. Metabolic acidosis is a known side-effect of the diet. Citrate has been mentioned as a substance that reduces symptoms of initial metabolic acidosis in ketogenic diet (Bergqvist et al. 2005). However, the dose used or the efficacy obtained has not been previously reported. Metabolic acidosis in renal diseases can be treated with citrate (Starke et al. 2012; Domrongkitchaiporn et al. 2002). Citrate is also used to prevent nephrolithiasis by counteracting urinary acidosis and hypocitraturia induced by ketogenic diet (Sampath et al. 2007). The antiepileptic effect of the diet is believed to depend of several mechanisms mediated by a fundamental shift from glycolysis to fatty acid and ketone body metabolism.

In this historical prospective controlled study we investigated the frequency of initial uncompensated metabolic acidosis in participants without, and with potassium citrate supplementation. The ketogenic diet was used as add-on treatment to children with drug resistant epilepsy. Potassium citrate was administered as oral Polycitra K crystals, 2 mEq/kg/day up to a maximum dose of 60 mEq/day. We evaluated the proportion of participants with >50 % seizure frequency reduction after 7 months.

The frequency of acidosis was investigated in 51 participants, 27 boys and 24 girls. None of the 22 participants with, and 10 of 29 (34%) without potassium citrate supplementation developed metabolic acidosis, odds ratio < 0.04 (95 % confidence interval 0.00-0.75 [p < 0.01]), median pH 7.32 vs. 7.24 (p < 0.001), and bicarbonate 19.7 mmol/l vs 14.0 mmol/l (p < 0.001). Serum beta-hydroxybuturate concentrations were independent of potassium citrate supplements. Seizure frequency was reduced with >50 % in 8/29 (28 %) participants without and 9/22 (41 %) with potassium citrate supplementation 7 months after introducing ketogenic diet (p = 0.4).

We found that supplementation with potassium citrate in ketogenic diet prevented uncompensated metabolic acidosis and, as expected, had an alkalizing effect in serum. Potassium citrate did neither interfere with the antiepileptic efficacy of the ketogenic diet, nor with serum levels of betahydroxybuturate. Our result could be of special interest in an out-patient setting where it is important to avoid metabolic acidosis.
 Thus, potassium citrate can be used as supplementation to ketogenic diet, not only to prevent nephrolithiasis, but also to prevent initial symptoms and side effects related to metabolic acidosis without reducing ketonemia and antiepileptic efficacy of the ketogenic diet. Seizure reduction by the diet in our study is within the range described in earlier studies (Martin-McGill et al. 2018). Further studies should be done to investigate how citrate affects chronic low-grade metabolic acidosis documented in ketogenic diet (Yancy et al. 2007)since even low grade compensated metabolic acidosis has side-effects such as kidney stone formation, increased bone resorption, reduced bone mineral density and loss of muscle mass(Carnauba et al. 2017).

P15 Electrical Stimulations of the Human Insula based on Brainnetome Atlas

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Stereotactic stimulations of the insular cortex through intracranial electrodes reproduce the ictal symptoms observed during the insular seizures. Multiple symptoms including somatosensory responses, visceral sensations and auditory sensations were evoked by insular stimulations in previous studies. However, the spatial segregation of these symptoms was usually represented by anatomical insular gyri or roughly anterior and posterior insula. The different insular response modalities may present clear functional segregation according to cytoarchitectonic maps such as the human Brainnetome Atlas based on connectional architecture.

The results of insular stimulations performed in 42 patients admitted between 2014 and 2018 for presurgical SEEG exploration were analyzed retrospectively. Stimulations (50 Hz, trains of 5 seconds, pulses of 0.3 ms, intensity 0.2–3.0 mA) were carried out using transopercular orthogonal electrodes or oblique electrodes implanted through frontal lobe or parietal lobe. All the intracranial electrodes were automatically and precisely extracted using pre-operative MRI and post-operative CT images via an integrative toolbox “FIELD”. The contacts coordinates were normalized to a standard MNI space and projected to Brainnetome Atlas. Six subregions were identified in the insular cortex according to the Atlas, including subregions G (hypergranular insula), vIa (ventral agranular insula), dIa (dorsal agranular insula), vId/vIg (ventral dysgranular and granular insula), dIg (dorsal granular insula), and dId (dorsal dysgranular insula).We regrouped the insular subregions into 3 groups:posterior dorsal group (G and dIg), anterior ventral group (vIa and dIa) and intermediate group (vId/vIg and dId).

411 contacts were located in the insular cortex and 176 contacts were clinical positive (42.82%).The highest response rate was located in subregion G(70/93,75.27%), and the lowest was subregion dIa (7/63,11.11%).In terms of response types, Most of the responses to insular stimulation were somatosensory sensations (n=78) that represented 44.32% of all evoked sensations, paresthesiae (n=60,34.09%), thermal sensations (n =11,6.25%), and pain (n =11,6.25%).Somatosensory sensations were obtained from posterior dorsal and intermediate group, and none from anterior ventral group. Specifically, the thermal and pain sensation were only obtain from posterior dorsal group. Visceral sensations represented the second major group of symptoms, as they were evoked in 34.66% (n =61).Contacts where stimulation evoked this type of sensation were broadly distributed over the insular cortex with except of subregion G. Interestingly, laryngopharyngeal symptoms among visceral sensations were mostly obtained from subregion dIg accounting for 70.59% of all this symtoms evoked in insular cortex. Auditory sensations were only obtained from subregion G. Psychic symptoms including déjà vu and anxiety only presented in anterior ventral group.

The present study may indicate a functional specificity for the insular cortex based on cytoarchitectonic segregation. Somatosensory and auditory sensations were maily located in posterior dorsal hypergranular and granular insula cortex especially for pain and thermal sensations. Laryngopharyngeal symptoms were maily located in dorsal granular cortex (subregion dIg). Psychic symptoms were only obtained from anterior agranular cortex. These findings contributed to the understanding of anatomofunctional organization and the role in epileptic network. Moreover, it could optimize the implantation strategy for exploring this multimodal representation cortex.

P16 Electrical features and seizure outcomes in patients with Focal Cortical Dysplasia and Non-Dysplastic Tissue: a SEEG study

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Focal Cortical Dysplasia (FCD) is the most frequent surgical remediable etiology in children. Two major categories are distinguished: FCD I and II. Some interictal and ictal electrophysiologic patterns have been described in different FCD. Nevertheless, the association between SEEG activity and histologic type, remains unclear especially for FCD I and non-dysplastic lesions as gliosis or normal cortex. The aim of the study is to compare interictal and ictal activity from Stereo-EEG recordings, in patients with FCD type I, II and gliosis, in order to investigate possible electrical biomarkers.

We reviewed all clinical, stereo-EEG and neuroimaging features of the 22, consecutively recruited patients from 2011 to 2017, with Cortical Dysplasia (FCD) or non-dysplastic lesion. FCD I was identified in 8, FCD type II in 10 and only gliosis in 4 patients. Interictal abnormalities were sub-grouped as focal, regional or extended and as continuous with a frequency from 1 to 10Hz or single random with a frequency < 1Hz. Ictal patterns were classified into three categories based upon morphology: burst suppression, spiking activity and fast activity.

Interictal patterns were analyzed in 22/22 patients: 7/8 patients with FCD I had single random abnormalities (87.5%) while 9/10 with FCD II had continuous abnormalities (90%) and 4/4 with gliosis had single random abnormalities (100%). Ictal patterns were analyzed in 20/22 patients: 5/6 patients with FCD I have only fast activity (83.3%) while in 7/10 patients with FCD II there was a preceding burst suppression pattern (70%) and in 4/4 patients with gliosis again only fast activity (100%).

Our data confirm the typical interictal and ictal pattern of FCD type II with repetitive interictal high frequency focal abnormalities and an ictal burst suppression pattern. We didn't find any difference between FCD I and non-dysplastic-tiissue.

P17 Propagation of seizures in a case of orbitofrontal cortex epilepsy studied by stereo-EEG

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Propagation of seizures originated from the orbitofrontal cortex is relatively rare and not well studied. We present one such case with SEEG to study the propagation of high-frequency oscillations before and after the EEG onset (peri-seizure initiation) using Multitapar time-frequency analysis.

The case was a 34-year-old, right-handed, MRI-negative male with 27 years of seizures and hypermotor symptomatology at night. SEEG electrodes were implanted, and the seizure onset zone(SOZ) was located in the right orbitofrontal cortex after visual analysis of SEEG recordings and EI analysis. The patient achieved seizure free at a follow-up time of 1.5 years after SEEG guided radio frequency thermocoagulation of the SOZ. Brainstorm software was used by the post-processing analysis to integrated the SEEG, imaging and electrode coordinates. EEG data was processed with Olivaer David's Multitapar time-frequency analysis method to extract the “baseline” and “peri-seizure initiation data” to obtain the time-frequency Z-score map.

The onset pattern was a burst of 18Hz high amplitude polyspikes lasting 8s followed by LVFA. Same as the visual analysis, the post-processing results demonstrated the high-frequency oscillation of obitofrontal cortex from 110-200 Hz band ($p<0.05$, z-score>3) for 8 seconds, with the patient showing no clinical manifestation; and then high-frequency oscillations occurred on the dorsal lateral prefrontal cortex and the cingulate gyrus, and the patient developed hypermotor movements.

Post-processing results and clinical observations are inseparable. Through time-frequency analysis, the positional changes of high-frequency abnormal oscillations and the correlation of clinical symptoms can be clearly reflected.

P18 Fenfluramine Reduces Convulsive Seizure Frequency in Dravet Syndrome Patients Receiving an Antiepileptic Drug Treatment Regimen Containing Stiripentol: A Phase 3, Randomised, Placebo-Controlled Clinical Trial

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Fenfluramine (FFA) has recently been shown in a Phase 3 clinical trial to reduce convulsive seizure frequency in patients with Dravet syndrome (DS) who were not treated with stiripentol (STP) compared to placebo. Here we report the results of a second Phase 3 clinical trial comparing FFA to placebo in patients with DS receiving an antiepileptic drug (AED) regimen including STP but still with poor seizure control.

Children and young adults (aged 2 to 18 years) with a diagnosis of DS who were receiving an AED regimen that included stable doses of STP were eligible for enrollment. Patients who demonstrated ≥6 convulsive seizures during the 6-week baseline period were randomly assigned to receive FFA 0.5 mg/kg/day (maximum 20 mg/day) or placebo. A dose of FFA 0.5 mg/kg/day provides comparable exposure to 0.8 mg/kg/day in patients not taking STP. After a 3-week blinded titration period, patients were maintained on their randomised dose for an additional 12 weeks. The number and type of seizures were recorded daily in an electronic diary by caregivers. The primary efficacy endpoint was the change in convulsive seizure frequency between FFA and placebo during the combined titration and maintenance periods compared with the baseline period.

A total of 87 patients (median age 9 years, range 2-19) were randomised in the study. The mean baseline convulsive seizure frequency across both groups was about 25 convulsive seizures per month. The study met its primary endpoint: patients treated with FFA (n=43) achieved a 54.7% greater reduction in monthly convulsive seizure frequency compared with placebo (n=44, P<0.001). FFA was also superior to placebo in both key secondary endpoints. In the FFA group, 53.5% demonstrated a clinically meaningful (≥50%) reduction in monthly convulsive seizures compared with 6.8% in the placebo group (P<0.001). The median longest seizure-free interval was 22 days in the FFA group compared with 13 days in the placebo group (P<0.005). Additionally, a profound (≥75%) reduction in monthly convulsive seizure frequency was achieved by 32.6% of the FFA group compared with 2.3% of the placebo group (P=0.004). The most common adverse events (AEs) were decreased appetite (44% FFA, 11% placebo), fatigue (26% FFA, 5% placebo), and diarrhea (23% FFA, 7% placebo). Discontinuations due to an AE occurred in 2 and 1 patients in the FFA and placebo groups, respectively. Prospective cardiac monitoring throughout the study demonstrated no clinical or echocardiographic evidence of cardiac valvular heart disease (VHD) or pulmonary hypertension.

FFA demonstrated robust efficacy in this Phase 3 trial in patients with DS on a current AED regimen that contained stable doses of STP. FFA was generally well tolerated, with no clinical and/or echocardiographic signs of cardiac VHD or pulmonary hypertension. FFA may represent an important and effective new treatment option for patients with DS.

P19 What Defines "Clinical Meaningful Changes in Seizure frequency"? Analysis of Data From a Phase 3 Clinical Trial of ZX008 in Dravet Syndrome

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A 50% reduction in seizure frequency is most often cited as clinically meaningful but is largely empirically derived. We set out to scientifically determine a clinically meaningful change in seizure frequency using data from a Phase 3, randomised, double-blind, placebo-controlled clinical trial of ZX008 (fenfluramine HCl oral solution) for the adjunctive treatment of seizures associated with Dravet syndrome (DS; Study 1); we utilised an anchor-based approach, examining percentage change in seizure frequency, and caregiver and investigator ratings of Clinical Global Impression of Improvement (CGI-I).

Patients with DS (N=119) were enrolled and randomised to placebo, ZX008 0.2 mg/kg/day, or ZX008 0.8 mg/kg/day (1:1:1) and entered a 2-week titration followed by a 12-week maintenance period (T+M). Study 1 met its primary endpoint, with patients in the ZX008-0.8 mg/kg/day group demonstrating a 63.9% greater reduction in seizure frequency vs the placebo group. After the 14-week T+M period, caregivers and investigators rated the change in clinical status from baseline using the CGI-I scale, a validated, 7-point scale with responses ranging from 1 (very much improved) to 7 (very much worse). Patients with CGI-I scores of 1 (very much improved) or 2 (much improved) were considered to have achieved a clinically meaningful response; a score of 3 (minimally improved) was not considered meaningful as most clinicians and caregivers desire a better response. The results of the three treatment groups were pooled for this analysis. The clinically meaningful percentage change in seizure frequency was estimated by receiver operating characteristic (ROC) analysis of binary CGI-I score vs percentage change in seizure frequency and defined as the cut-point for which specificity and sensitivity were equal or most similar.

CGI-I assessments were provided for 112 patients by caregivers and 114 patients by investigators. ROC analysis identified a 44% reduction in seizure frequency as the clinically meaningful cutoff point for both caregiver and investigator assessments. Based on this threshold, 75%, 46%, and 12.5% of patients in the ZX008-0.8 mg/kg/day, ZX008-0.2 mg/kg/day, and placebo groups, respectively, achieved a clinically meaningful reduction from baseline in seizure frequency in Study 1.

This analysis of the association between percentage change in seizure frequency and CGI-I rated by caregivers or investigators suggests that a 44% reduction from baseline in seizure frequency can be considered a clinically meaningful response in patients with DS. Notably, higher levels of seizure reduction (60%-68%) were associated with caregiver and investigator CGI-I ratings of "very much improved." Further analyses from other Phase 3 studies in DS and other patient populations should be performed to confirm these findings and explore other potential factors that contribute to caregiver and investigator CGI-I ratings, such as non-seizure outcomes and tolerability.

P20 Fenfluramine HCl Provides Long-Term Clinically Meaningful Reduction in Seizure Frequency: Results of an Open-Label Extension Study

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Fenfluramine (FFA) has demonstrated superior efficacy compared to placebo for the reduction in frequency of convulsive seizures in children and young adults (2-18 years old) with Dravet syndrome in two recently completed Phase 3 clinical trials. Here we report the preliminary interim analysis of the effectiveness and tolerability of FFA in a long-term open label extension study.

Dravet syndrome patients completing one of the Phase 3 clinical trials were eligible to enroll in the open-label extension (OLE) study. All patients entering the OLE initiated FFA at a dose of 0.2 mg/kg/day regardless of what dose they were receiving in the core trial. After 4 weeks, the dose could be titrated up in 0.2 mg/kg/day increments up to a maximum of 0.8 mg/kg/day [max 30 mg/day]; 0.5 mg/kg/day [max 20 mg/day] if patient was also on stiripentol. Effectiveness and safety were assessed at months 1, 2, and 3 and then 3-month intervals thereafter.

A total of 232 patients have enrolled in the study as of March 13, 2018. A total of 128 (55.2%) were male, and the mean±SD age was 9.1±4.7 years. A total of 22 (9.5%) patients discontinued treatment: lack of efficacy (16), subject withdrawal (2), adverse event (1), death (1, Sudden Unexpected Death in Epilepsy (SUDEP)), physician decision (1), and withdrawal by caregiver (1). Median duration of treatment with FFA was 256 days (range, 58-634 days). The median percent reduction in monthly convulsive seizure frequency over the entire OLE treatment period as compared with the baseline frequency established in the core Phase 3 studies was 66.8%. A clinically meaningful reduction in convulsive seizure frequency was noted at the first observation (month 1) during OLE and continued over time. Over the entire observation period, 64.4% of patients demonstrated a 50% reduction in convulsive seizure frequency and 41.2% demonstrated a 75% reduction. At 12 months 70.4% of caregivers and 77.8% of investigators rated patients as "much improved" or "very much improved." The most common non-cardiovascular adverse events occurring in ≥10% of patients were pyrexia (21.6%), nasopharyngitis (19.4%), decreased appetite (15.9%), influenza (11.6%), diarrhoea (10.8%), and upper respiratory infection (10.3%). No patient had any echocardiographic or clinical signs of cardiac valvular heart disease or pulmonary hypertension at any time during this OLE.

The preliminary results of this interim analysis of a long-term, OLE study demonstrate that FFA continues to provide clinically meaningful and substantial reductions in convulsive seizure frequency over extended periods of time; while being generally well tolerated. FFA represents a novel, highly effective antiepileptic treatment option for patients with Dravet syndrome.

P21 Long-Term Cardiovascular Safety of Fenfluramine HCl in the Treatment of Dravet Syndrome: Interim Analysis of an Open-Label Safety Extension Study

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In two recently completed Phase 3 clinical trials, fenfluramine has demonstrated superior efficacy compared with placebo for the reduction of convulsive seizures in children and young adults (2-18 years old) with Dravet syndrome. Fenfluramine, previously marketed for weight loss, was withdrawn from the market in 1997 following reports of cardiac valvular heart disease (VHD) and pulmonary hypertension in obese adults treated with ≥60 mg/day. Here we report the cardiovascular safety findings from an interim analysis of the long-term safety extension study of low-dose fenfluramine for the treatment of Dravet syndrome in children and young adults.

Patients with Dravet syndrome who successfully completed one of the Phase 3 trials were eligible to enroll in this open-label extension (OLE) study. Patients with current cardiac VHD, pulmonary arterial hypertension, or any degree of aortic or mitral valve regurgitation were excluded from entering any of the Phase 3 trials. All patients in the OLE were started on fenfluramine at 0.2 mg/kg/day, and after 4 weeks the dose could be titrated in 0.2 mg/kg/day increments every 2 weeks based on effectiveness and tolerability up to a maximum of 0.8 mg/kg/day but not to exceed 30 mg/day (0.5 mg/kg/day and 20 mg/day if they were taking concurrent stiripentol). Echocardiography was performed at extension study baseline, Week 6, and every 3 months thereafter to assess cardiac valve function and pulmonary artery pressure. Cardiac VHD was defined as the presence of ≥ moderate mitral regurgitation and/or ≥ mild aortic regurgitation. Pulmonary hypertension was considered to be present when pulmonary artery systolic pressure exceeded 35 mmHg.

A total of 232 patients enrolled in the study as of the interim cutoff date of March 13, 2018 and received at least one dose of fenfluramine. Twenty-two (9.5%) patients have discontinued treatment due to: lack of efficacy (16), subject withdrawal (2), adverse event (1), death (1, Sudden Unexpected Death in Epilepsy (SUDEP)), physician decision (1), or withdrawal by caregiver (1). Demographics include 128 (55.2%) male patients and a mean±SD age of 9.1±4.7 years. The median duration of treatment with fenfluramine was 256 days (58-634 days). No patient demonstrated cardiac VHD or pulmonary arterial hypertension at any time during the study. The most common finding was intermittent and transient physiologic/trace valve regurgitation, a finding seen in normal healthy children and young adults.

The results of this long-term safety study demonstrate no development of cardiac VHD or pulmonary hypertension after daily treatment with fenfluramine for up to 21 months in patients with Dravet syndrome. Together with the efficacy data from the Phase 3 trials, fenfluramine appears to have a positive benefit-risk profile in this patient population.

P22 Perampanel in real-world clinical care of patients with epilepsy: retrospective, Phase IV Study 506

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Perampanel is a once-daily oral anti-seizure drug for partial-onset seizures and primary generalised tonic-clonic seizures. Real-world, retrospective studies can provide information on the effectiveness, safety, tolerability and characteristics of a drug or device, outside the relative confines of a clinical efficacy study. Here, we report third interim results of the multicentre, non-interventional, Phase IV, retrospective Study 506 (NCT03208660) to assess retention rate, safety and dosing experience of perampanel administered to patients with epilepsy during routine clinical care.

Exposure, safety and efficacy data were obtained from medical records of patients initiating perampanel after 1 January 2014. The primary endpoint is retention rate (proportion of patients in the Safety Analysis Set remaining on perampanel at 3, 6, 12, 18 and 24 months). Safety, efficacy and dosing experience are secondary objectives.

The interim Safety Analysis Set (N=1118; 54.4% female) included 776 (69.8%) patients aged ≥18 years, 152 (13.7%) aged <12 years, and 184 (16.5%) aged 12 to <18 years (data unavailable: 6 patients); mean (standard deviation [SD]) age was 29.1 (16.6) years. At data cut-off (10 October 2018), 591 (52.9%) patients remained on perampanel; 522 (46.7%) had discontinued. Most common reasons for discontinuation were adverse events (n=244 [21.8%]) and inadequate therapeutic effect (n=143 [12.8%]). Mean (SD) cumulative duration of exposure to perampanel was 17.7 (15.5) months. Mean (SD) maximum perampanel dose was 6.7 (3.2) mg. Retention rates at 3, 6, 12, 18 and 24 months were 82.1% (n=910/1108), 72.1% (n=774/1074), 61.2% (n=586/957), 54.6% (n=448/820) and 52.4% (n=343/655), respectively. At Months 22–24, median reduction in seizure frequency per 28 days was 98.3% (n=34), 50% responder rate was 76.5% (n=26/34), and 47.1% (n=16/34) of patients achieved seizure freedom. Treatment-emergent adverse events (TEAEs) were reported in 490 (43.8%) patients; most common were dizziness (n=104 [9.3%]), aggression (n=61 [5.5%]) and irritability (n=50 [4.5%]). TEAEs leading to perampanel dose adjustments occurred in 391 (35.0%) patients. Serious TEAEs occurred in 27 (2.4%) patients, including 4 (0.4%) deaths.

This interim analysis further defines the safety profile and demonstrates favourable retention rates and sustained efficacy of perampanel for up to 2 years in patients with epilepsy treated during routine clinical care. Funding: Eisai Inc.

P23 Study 506 – a retrospective, Phase IV study of perampanel in real-world clinical care of patients with epilepsy: adolescent subgroup (aged 12 to <18 years)

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Perampanel is a once-daily oral anti-seizure drug for partial-onset seizures (POS) and primary generalised tonic-clonic seizures (PGTCS). Real-world, retrospective studies can provide information on the effectiveness, safety, tolerability and characteristics of a drug or device, outside the relative confines of a clinical efficacy study. Here, we report third interim results of the multicentre, non-interventional, Phase IV, retrospective Study 506 (NCT03208660) to assess retention rate, safety and dosing experience of perampanel administered to adolescent patients (aged 12 to <18 years) with epilepsy during routine clinical care.

Study 506 is enrolling patients who initiated treatment with perampanel after 1 January 2014. Data were obtained retrospectively from medical records. The primary endpoint is retention rate (proportion of patients in the Safety Analysis Set remaining on perampanel at 3, 6, 12, 18 and 24 months). Safety, efficacy and dosing experience are secondary objectives.

The interim Safety Analysis Set (N=1118) included 184 patients aged 12 to <18 years (mean [standard deviation (SD)] age, 14.7 [1.7] years; female, 48.9%; mean [SD] age at epilepsy diagnosis, 6.0 [5.0] years; mean [SD] time since epilepsy diagnosis, 9.3 [5.0] years). Seizure types included: complex partial, n=94 (51.6%); POS with secondary generalisation, n=57 (31.3%); and PGTCS, n=92 (50.5%). The mean (SD) perampanel dose received was 5.8 (2.9) mg. The mean (SD) maximum perampanel dose was 6.9 (3.3) mg. At data cut-off (10 October 2018), 100 (54.3%) adolescent patients remained on perampanel; 83 (45.1%) had discontinued. Primary reasons for discontinuing included adverse events (AEs; n=38 [20.7%]) and inadequate therapeutic effect (n=25 [13.6%]). Retention rates at 3, 6, 12, 18 and 24 months were 81.0% (n=149/184), 74.0% (n=134/181), 63.4% (n=104/164), 59.1% (n=78/132) and 62.1% (n=64/103), respectively. Treatment-emergent AEs were reported in 41.8% of patients; most common were somnolence (8.2%), aggression (7.1%) and dizziness (6.5%).

An interim subgroup analysis of the real-world Study 506 suggests daily oral doses of adjunctive perampanel are generally well tolerated, with favourable retention rates for up to 2 years in adolescent patients aged 12 to <18 years with epilepsy. Funding: Eisai Inc.

P24 Study 506 – a retrospective, Phase IV study of perampanel in real-world clinical care of patients with epilepsy: paediatric subgroup (aged <12 years)

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Perampanel is a once-daily oral anti-seizure drug for partial-onset seizures and primary generalised tonic-clonic seizures (PGTCS). Real-world, retrospective studies can provide information on the effectiveness, safety, tolerability and characteristics of a drug or device, outside the relative confines of a clinical efficacy study. Here, we report third interim results of the multicentre, non-interventional, Phase IV, retrospective Study 506 (NCT03208660) to assess retention rate, safety and dosing experience of perampanel administered to paediatric patients (aged <12 years) with epilepsy during routine clinical care.

Data were obtained from medical records of patients initiating perampanel after 1 January 2014. The primary endpoint is retention rate (proportion of patients in the Safety Analysis Set remaining on perampanel at 3, 6, 12, 18 and 24 months). Safety, efficacy and dosing experience are secondary objectives.

The interim Safety Analysis Set comprised 1118 patients, of whom 152 were aged <12 years (mean [standard deviation (SD)] age, 6.9 [3.1] years; female, 52.6%; mean [SD] age at epilepsy diagnosis, 2.5 [2.8] years; mean [SD] time since epilepsy diagnosis, 5.1 [3.3] years). Seizure types included: complex partial, n=75 (49.3%); PGTCS, n=66 (43.4%); myoclonic, n=58 (38.2%). Perampanel was titrated as follows: weekly (18.4% of patients); every 2 weeks (25.0%); every 3 weeks (2.6%); 'other' (36.2%); 'unknown' (17.8%). Mean (SD) cumulative duration of exposure to perampanel was 17.7 (16.0) months. Mean (SD) maximum perampanel dose was 5.1 (2.8) mg. At data cut-off (10 October 2018), 80 (52.6%) paediatric patients remained on perampanel; 71 (46.7%) had discontinued. Primary reasons for discontinuing included adverse events (AEs; n=25 [16.4%]) and inadequate therapeutic effect (n=25 [16.4%]). Retention rates at 3, 6, 12, 18 and 24 months were 83.6% (n=127/152), 71.4% (n=105/147), 63.3% (n=81/128), 55.8% (n=58/104) and 53.7% (n=44/82), respectively. Treatment-emergent AEs were reported in 34.9% of patients; most common were aggression (5.9%), irritability (4.6%) and somnolence (4.6%).

An interim subgroup analysis of the real-world Study 506 suggests daily oral doses of adjunctive perampanel are generally well tolerated, with favourable retention rates for up to 2 years in paediatric patients aged <12 years with epilepsy. Funding: Eisai Inc.

P25 Incidence, etiology and clinical characteristics of epilepsy presenting in the first two years of life. A Swedish population-based study.

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Population-based data on early-onset epilepsy are scarce. With the availability of a prospective incidence registry of epilepsy and new diagnostic possibilities our aim with this study is to give a population-based overview of etiology and clinical characteristics of epilepsy presenting before two years of age and to calculate incidence.

The prospective Stockholm Incidence Registry of Epilepsy (SIRE) aims to register in Northern Stockholm all cases of a first unprovoked seizure leading to medical attention and diagnosis. On all children registered before two years of age during the study period 01/09/2001-31/12/2006, information on symptoms, work-up and etiology were retrieved from medical records. All children with epilepsy in the area are managed at the Karolinska University Hospital. In cases of epilepsy with unknown etiology work-up was updated according to present practices including whole exome/genome sequencing where appropriate. Descriptive statistics was applied and overall and syndrome-specific incidences were calculated.

Cases were classified based on all information available until age seven using the latest ILAE epilepsy definition and listed epilepsy syndromes. A first unprovoked epileptic seizure before age two was registered in 139 children during the study period. In retrospect, 116 children (83%) fulfilled epilepsy criteria before age seven corresponding to an incidence of 87/100.000. 88 of 116 children (76%) with epilepsy had onset during the first year of life, the incidence being 133/100.000. Mean age at epilepsy diagnosis documented in the medical records was 6 months (average 9.2), on average 1.8 months after the first unprovoked seizure. Females constituted 49% of epilepsy before two years. 16% of children had a first degree relative with epilepsy. In 14 cases history revealed seizures before the first registered seizure, on average nine weeks before. Of the first unprovoked seizures 46% were focal, 6% generalized, 21% spasms and 28% unclassified. Until seven years of age 83 children (72%) had only had one seizure category (45 focal, 6 generalized, 12 spasms, 20 unclassified). The other 33 had different combinations. 15 (13%) had status epilepticus. The most common epileptic encephalopathies were West syndrome in 33 children (28%) and Lennox-Gastaut in 10 (9%). Epilepsy in infancy with migrating focal seizures was found in 2 cases, Dravet syndrome in only 1 case, Ohtahara syndrome and early myoclonic encephalopathy in none. After completed work-up 68 cases (59%) had a revealed etiology. Most common were cerebral malformations in 16 cases (6 with genetic diagnosis), metabolic disease in 10 (7 with genetic diagnosis) and birth asphyxia in 10. Of West syndrome cases 73% had a proven etiology. Altogether 31 cases (27%) had a genetic diagnosis of which 25 were monogenic. The yield in 18 performed whole exome/genome sequencing diagnostics was 67%. Earlier epilepsy onset was related to higher genetic yield (71% <12 months vs 20% >12 months).

This study gives a population-based map of early onset epilepsy. The etiological diagnostic yield can be significantly increased by the use of next generation sequencing. A later report will describe prognostic factors, treatment and outcome in the same cohort of children.

P26 Posterior cortex epilepsy in children: etiology, semiotics and surgery

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A single-institution experience of surgical treatment in children with posterior cortex epilepsy is presented aiming to examine seizure semiotics and the outcome after surgical treatment as well

All data including the history of disease, video-EEG recordings and imaging of children under 18 with posterior cortex epilepsy who underwent surgery were extracted from prospectively collected institutional epilepsy surgery database and reviewed. Sixty-eight consecutively operated children (29 females; 39 male) were identified. An at least 6 months of follow-up was among inclusion criteria besides the age and drug-resistant posterior cortex structural epilepsy. The most frequent etiological substrate was focal cortical dysplasia (35 patients) followed by the neuro-glial tumors (18), cavernous malformations (5), gliosis (5), Sturge-Weber disease (4) and tuberose sclerosis in 1 case. The right side was affected in 35 children, 33 patients had a left-sided lesions. Nine children underwent an extended tailored resection in the occipito-parietal region; in 3 cases the resection involved the neighboring occipito-temporal cortices and in 2 patients a rather large resection was performed within parieto-temporal region. In the remaining 16 cases the procedure involved the whole temporo-parieto-occipital area (TPO-disconnection). Six patients needed second surgery because of relapse and/or persisting seizures. Postop evaluation included physical and neurological exams, video-EEG and MRI. Follow-up is available in all patients: median – 16 months.

The common initial ictal symptoms were visual auras followed by oculomotor signs. Two different scenarios were noted further, either an axial deviation of the head followed by a hemiclonic or versive seizures: 40 cases (59%) which usually corresponded to parietal lobe lesions, or autonomic/vegetative manifestations and oro-alimentary automatisms: 9 patients (13%), characteristic for patients with principally occipital lobe lesions. EEG (both interictal and ictal) was helpful do localize ictal onset zone in majority of cases, but failed in 12 patients (18%) showing either bi-hemispheric spiking or only frontal lobe focuses. Forty five patients were free of seizures (Engel outcome score I) at the last check (66%). Complications were noted in 26 cases: hemiparesis temporary – in 11 cases; persistent - in 5. Hemianopia (anticipated) was noted in 8 patients.

Seizures originating in posterior cortex have variable semiology which reflect lesion localization and existing network to expand. In patients with focuses in cuneus and lateral occipital-posterior temporal area epileptic activity propagate mostly to the temporal lobe and/or insula presenting with automotor and vegetative symptoms; those with focuses in praecuneus and/or within dorsal occipito-parietal region often exhibit contralateral motor (tonic/clonic) seizures. Both ictal and interictal scull EEG data may be misleading because of rapid propagation of seizure activity anteriorly and to the contralateral hemisphere. Visual auras are a valuable ictal sign but some patients, particularly younger kids may not report it. MRI and careful assessment of all electro-clinical data are essential in maintaining true diagnosis. Up to 2/3 of patients with structural posterior cortex epilepsy may benefit from surgery and rendered free of seizures if carefully selected and appropriately studied.

P27 Ictal intracranial EEG findings in a in a child with typical Lennox-Gastaut syndrome successfully treated by surgery

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Lennox-Gastaut Syndrome (LGS) is a severe refractory epileptic syndrome of childhood, characterized by (1) interictal diffuse slow spikes-wave complexes (SSW) at <3Hz and paroxysmal fast activity (PFA), (2) multiple generalized seizure types including tonic, atonic and atypical absences seizures and (3) cognitive impairment. In two third of patients, structural or genetic cause is identified. When a localized structural lesion is present on MRI, some cases of seizure freedom after lesionectomy have been reported. In functional MRI studies, distinct networks are involved during PFA (activation of association cortex, thalamus and brainstem) and SSW (mainly diffuse cortical deactivation, sometimes thalamic activation, no brainstem involvement). It is hypothesized that a focal lesion could drive these diffuse epileptic networks. We report intracranial EEG findings in a 6-year-old girl with typical LGS, successfully treated by right frontal lobe disconnection.

The child had no particular personal history before epilepsy onset. At five years, in July 2015, she presented with non-motor seizures with automatisms and clusters of spasms. Interictal EEG showed multifocal spike-waves. Six months later she developed LGS with daily atypical absences, absence status, tonic seizures and tonic spasms leading to falls, associated with cognitive decline and behavioral disorders. Long-term video-EEG has recorded tonic seizures with diffuse PFA, mostly during sleep and atypical absences with diffuse SSW, sometimes followed by multifocal spikes (temporal bilateral, frontal right > left and on the midline). Genetic and metabolic investigations were negative. First brain MRI showed no clear abnormality. Brain FDG-PET revealed a large temporal bilateral hypometabolism predominating to the left, and a more discreet metabolic decrease in right frontal lobe. A second MRI detected subtle right prefrontal abnormality possibly compatible with a focal cortical dysplasia, without clear lesional limits. We performed an intracranial EEG to explore the right frontal lobe: two subdural grids (fronto-polar and prefrontal / premotor superior and middle frontal gyri) and three depth electrodes (orbito-frontal cortex, anterior cingulate gyrus, mesial superior frontal gyrus and supplementary motor area).

Intracranial EEG showed focal fast activity in right fronto-polar cortex approximately two seconds before tonic seizures clinical onset. This focal activity was not detectable on surface EEG. On the other hand, no focal ictal activity was observed during or right before atypical absences. Right broad fronto-polar disconnection was performed in March 2017. Twenty three months later, the patient is still seizure free. Learning abilities and behaviour are markedly improved. Generalized interictal epileptic discharges have progressively regressed on EEG one and two months after surgery, and completely disappeared after three months (« running down phenomenon »).

We confirm that typical LGS can be successfully treated by focal surgery, leading to seizure freedom and stopping the encephalopathic process. Intracranial EEG may be useful in selected cases. In this case, ictal intracranial EEG shows that cortical focal discharge has triggered the diffuse network involved in tonic seizures. Atypical absence seems to imply a different mechanism, without ictal focal cortical activity detected during this seizure type.

P28 Safety and efficacy of adjunctive perampanel in paediatric patients (aged 4 to <12 years) with partial-onset seizures or primary generalised tonic-clonic seizures: final results from the 311 Core Study

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In younger patients with epilepsy (≥4 years of age), interventional, placebo-controlled clinical studies may not be required if the efficacy data from completed studies in adults and adolescents with epilepsy can be extrapolated to children, and where a similar exposure–response relationship between adults and children can be demonstrated. In contrast, safety data cannot be extrapolated from adults to children; therefore, separate (open-label) clinical studies are required to assess safety in the ≥4-years-of-age group. Perampanel is a once-daily oral anti-seizure drug for partial-onset seizures (POS) and primary generalised tonic-clonic seizures (PGTCS). Study 311 (NCT02849626) was a global, multicentre, open-label, single-arm study designed to assess the safety, tolerability, pharmacokinetics and efficacy of once-daily adjunctive perampanel oral suspension in paediatric patients aged 4 to <12 years with POS (with/without secondarily generalised seizures [SGS]) or PGTCS. The 311 Core Study has now completed, and here, we present the final safety and efficacy data.

The Core Study consisted of a 4-week Pre-treatment Period (Screening/Baseline), 23-week Treatment Period (11-week Titration; 12-week Maintenance) and a 4-week Follow-up Period. The primary endpoint was assessment of safety and tolerability of perampanel in children aged 4 to <7 years and 7 to <12 years with POS (with/without SGS) or PGTCS. Secondary endpoints included median percent change in seizure frequency per 28 days from Baseline during the Treatment Period (Titration and Maintenance Periods) of the Core Study, and 50% responder and seizure-freedom rates during the Maintenance Period of the Core Study and long-term treatment (≤52 weeks).

In total, 180 patients (POS, n=149; SGS, n=54; PGTCS, n=31) received ≥1 dose of perampanel (mean [standard deviation (SD)] age, 8.1 [2.1] years; female, 48.9%). Of these, 146 (81.1%) patients completed the Core Study and 34 (18.9%) had discontinued. The most common primary reason for discontinuation was adverse event (AE; n=14 [7.8%]). The mean (SD) daily dose of perampanel was 7.0 (2.6) mg/day; median (range) duration of exposure was 22.9 (0, 27) weeks. Treatment-emergent AEs occurring in ≥10% of patients were: somnolence, nasopharyngitis, dizziness, irritability, pyrexia and vomiting. Median percent reductions in seizure frequency per 28 days were 40.1% in patients with POS, 58.7% in patients with SGS, and 69.2% in patients with PGTCS. Corresponding 50% responder and seizure-freedom rates, respectively, were 46.6% and 11.5% in patients with POS, 64.8% and 18.5% in patients with SGS, and 63.6% and 54.5% in patients with PGTCS.

Adjunctive perampanel was generally safe, well tolerated and efficacious in children aged 4 to <12 years with POS (with/without SGS) or PGTCS. Funding: Eisai Inc.

P29 Safety and efficacy of adjunctive perampanel in younger (aged 4 to <7 years) and older (7 to <12 years) paediatric patients with partial-onset seizures or primary generalised tonic-clonic seizures: final results from the 311 Core Study

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In younger patients with epilepsy (≥4 years of age), interventional, placebo-controlled clinical studies may not be required if the efficacy data from completed studies in adults and adolescents with epilepsy can be extrapolated to children, and where a similar exposure–response relationship between adults and children can be demonstrated. In contrast, safety data cannot be extrapolated from adults to children; therefore, separate (open-label) clinical studies are required to assess safety in the ≥4-years-of-age group. Perampanel is a once-daily oral anti-seizure drug for partial-onset seizures (POS) and primary generalised tonic-clonic seizures (PGTCS). Study 311 (NCT02849626) was a global, multicentre, open-label, single-arm study designed to assess the safety, tolerability, pharmacokinetics and efficacy of once-daily adjunctive perampanel oral suspension in paediatric patients aged 4 to <12 years with POS (with/without secondarily generalised seizures [SGS]) or PGTCS. Here, we report final safety and efficacy data from the 311 Core Study stratified by age: 4 to <7 years and 7 to <12 years.

The Core Study consisted of a 4-week Pre-treatment Period (Screening/Baseline), 23-week Treatment Period (11-week Titration; 12-week Maintenance) and a 4-week Follow-up Period. The primary endpoint was assessment of safety and tolerability of perampanel in children aged 4 to <7 years and 7 to <12 years with POS (with/without SGS) or PGTCS. Secondary endpoints included median percent change in seizure frequency per 28 days from Baseline during the Treatment Period (Titration and Maintenance Periods) of the Core Study, and 50% responder and seizure-freedom rates during the Maintenance Period of the Core Study and long-term treatment (≤52 weeks).

In total, 180 patients received ≥1 perampanel dose. In the Safety Analysis Set (4 to <7 years, n=46; 7 to <12 years, n=134), 45 (97.8%) and 115 (85.8%) patients, respectively, reported treatment-emergent adverse events; the most common (≥10%) were somnolence, nasopharyngitis, dizziness, irritability and vomiting. Median percent reductions in seizure frequency per 28 days for POS, SGS and PGTCS, respectively, were: 42.7%, 56.3% and 56.5% in patients aged 4 to <7 years; and 40.1%, 60.6% and 81.9% in patients aged 7 to <12 years. Fifty percent responder rates were similar for POS (18/40 [45.0%] vs 51/108 [47.2%]) and SGS (12/17 [70.6%] vs 23/37 [62.2%]) or PGTCS (2/3 [66.7%] vs 12/19 [63.2%]) in the younger vs older age cohorts, respectively. Seizure freedom was achieved in 3/40 (7.5%) vs 14/108 (13.0%) patients with POS, 3/17 (17.6%) vs 7/37 (18.9%) patients with SGS and 2/3 (66.7%) vs 10/19 (52.6%) patients with PGTCS in the younger vs older age cohorts, respectively.

These data suggest adjunctive perampanel was generally well tolerated and efficacious in paediatric patients aged 4 to <7 years and 7 to <12 years with POS (with/without SGS) or PGTCS. Funding: Eisai Inc.

P30 Surgery throws new light on a SCN 8A-related epilepsy treatment: a case report.

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Mutations in SCN8A are associated with Early infantile epileptic encephalopathy and severe cognitive impairment. Antiepileptic drugs acting on sodium channel have been documented to be partially effective in controlling seizures but otherwise there are no other effective treatment.

We report a child with SCN8A-related epilepsy with coexisted focal cortical dysplasia (FCD) who had a remarkable improvement following successful epilepsy surgery.

A 2-year-old girl with SCN8A-related epilepsy and developmental delay had an onset of epilepsy at 3 months of age. She started having clusters of seizures consisting of impaired consciousness and legs clonic activities occurring up to 50-60 times daily. Despite treatment with various combinations of carbamazepine, phenytoin, valproic acid, levetiracetam, topiramate, and perampanel, her seizures still progressively worsened. Brain MRI showed evidence of FCD at the right mesial frontal lobe. EEG demonstrated ictal onset arising from the bilateral frontocentral regions. In light of FCD causing severe epilepsy in patients with underlying genetic etiology, we decided to perform subdural grid implantation and lesionectomy on this patient. Pathology revealed FCD type IIA. After surgery, her seizures were 50-60% improved. Follow-up postoperative EEG showed frequent epileptiform discharges over the right posterior rim of an old lesion as well as the left frontal region. One year later, she underwent SEEG implantation covering bilateral frontal regions followed by resection of the right frontocentral region. At the end of 1 year and 11 months follow up, she continued to experience significant seizure improvement (Engel class II). In addition, her development continues to progress remarkably.

Intractable epileptic patients with underlying genetic etiologies are likely to defer surgery despite failure to many antiepileptic drugs which lead to profound neurocognitive deterioration. Epilepsy surgery could be an alternative option in selected patients, especially in patients who demonstrate focal cortical dysplasia offering the opportunity of marked seizure improvement as well as the quality of life in this group.

P31 SEEG guided Radio Frequent ThermoCoagulation in Epilepsy due to periventricular heterotopias: single center experiences

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In a selected refractory epilepsy patient group pre-surgical analysis encompasses Stereo-EEG (SEEG): invasive EEG with multiple depth electrodes. When contact points prove to be in the seizure onset zone, it is possible to use the same electrodes to perform a local Radio Frequent Thermo-Coagulation (RFTC) by locally administering a high-output current. In our center we started in 2016 performing RFTC in patients with periventricular (multi)nodular heterotopias (PVNH), extending the indication to focal onset without MRI abnormalities end 2018. We here describe our results in patents with PVNH.

All consecutive adult patients with refractory focal epilepsy and PVNH enrolled in our epilepsy surgery program were included. If SEEG indicated PVNH-involvement in seizure onset, all involved contact points were coagulated (50 Hz 50V output during 30 seconds). Subsequently recording was restarted for 4 hours. If in the coagulated or nearby contact points within the PVNH epileptiform grapho-elements were still recorded these were (re)coagulated. There-after patients were transferred to the neurosurgical department for explantation of the electrodes. Side effects and effect on seizure frequency and severity were noted. If no permanent seizure freedom was obtained patients were evaluated for resective surgery.

12 Patients were enrolled in this study. As one patient was re-evaluated once, and two patient twice, in total 16 complete procedures were performed. The PVNH's are distributed along the ventricles, resulting in a divers pattern of both surface EEG and semiology. In five patients, the PVNH was local, in the others there were multiple PVNH,s either unilateral or bilateral. In all patients at least the PVNH was involved in seizure onset. In most seizures the onset was visible in the PVNH but the subsequent seizure did not any more involve the PVNH. Number of coagulated contact points ranged from 1 to 34. 6 patients are seizure free up to now, with a follow up ranging from 3 to 33 months. One additional patient might be free from epileptic seizures but developed psychogenic seizures (PNEA), whereas in 2 patients a seizure frequency reduction of >80% is reached,of whom one after a third procedure. Most coagulations resulted in incomplete lesioning of the PVNH, with only 3 complete coagulations. Of the seizure free patients, the PVNH was completely lesioned in 1 out of 5, one patient with probably PNEA underwent a complete lesioning and one out of two patients with >80% seizure reduction underwent a complete lesioning. Meaning that 4 out of 5 seizure free patients underwent an incomplete lesioning of mostly widespread PVNH's. There were no complications due to the RFTC in our group.

Despite several reports showing that in PVNH the overlying cortex might be more important and that incomplete lesioning is not fruitful, our results tend to favor the notion that destruction of the critical hub(s) in the PVNH as part of the epileptogenic network can be sufficient to obtain seizure freedom at low cost and low risk. Therefore, all patients with PVNH, including those with dual pathology, should be offered SEEG and RFTC.

P32 The case of Dravet syndrome with truncating mutation of SCN1A

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More than 1000 pathogenic mutations of SCN1A, the gene coding for the NaV1.1 voltage gated sodium channel, have been identified thus far [1] and can cause well defined epilepsies[2], but genotype-phenotype correlation and selection of therapies are still challenging[3]. SCN1A mutations cause Dravet syndrome (DS) and GEFS+ (which is in general milder), and are risk factors in other epilepsies[4]. It is generally considered that an SCN1A truncating mutation causes the severe phenotype of Dravet syndrome. Dravet syndrome is an intractable epileptic encephalopathy, which occurs during the first year of life. The condition appears during the first year of life as frequent fever-related (febrile) seizures.[1] A family history of either epilepsy or febrile seizures exists in 15 percent to 25 percent of cases[6]. Intellectual development begins to deteriorate around age 2, and affected individuals often have a lack of coordination, poor development of language, hyperactivity, and difficulty relating to others[7,8]. Although the seizures are intractable, the interictal electroencephalography (EEG) remains free of epileptic discharges during the first year of life[9]. Later, generalized spikes and waves occur, with photosensitivity and focal abnormalities.

2-year-old female patients at the time was born to non-consanguineous healthy parents at term, with a normal birth weight, after an uneventful pregnancy. His family history was unremarkable. At 6 months of age, he experienced a prolonged FS lasting about 5 min. Attempts to prevent FS using a diazepam 2.0ml i/m failed, and valproic acid (VPA) was administered. VPA 120mg 2 times per day did not control the multiple FS. At the age of 6 months, EEG revealed amplification of lateral signals on both sides. Patient was hospitalized to Neurological department. At the age of 8 months, EEG expressed diffuse disorganization and slowing cortical rhythm; Sleep is modulated in stages and phases. Epileptiform activity is recorded only during sleep of a single character, represented by single sharp waves regionally in the left frontal area with a tendency to spread along the left central frontal-temporal leads(Pic.1). Magnetic resonance imaging (MRI), Neurosonography revealed no brain abnormality. At the age of 12 months, VPA was changed to Levetiracetam 450 mg per day and Topiramate18.75 mg due to developed thrombocytopenia, however FS continue on subfebrile and febrile temperature. For a year period was hospitalized 12 times. At the age of 24 months, MRI revealed focal gliosis changes in the white matter of the frontal region of posthypoxic genesis, sclerosis of the left hippocampus(Pic.2). Therapy scheme was altered to Ethosuximide 320mg per day , Stiripentol 500mg per day, Clobazam 5 mg per day, however has not decreased seizure frequency. Seizures occur on afebrile temperature, about 3 times per week.

PCR DNA sequencing was performed for all of the exons and intron-exon boundaries of SCN1A (NM_006920.4), according to the Guangzhou University database. The mutation was not registered in the control samples of "1000 genomes", ESPN6500 and ExAC(Tab. 1,2).

This report describes patient presenting with Dravet syndrome with a truncation mutation of SCN1A. It is generally considered that SCN1A truncating mutations cause the severe phenotype of Dravet syndrome [3], although around 10% of patients with GEFS+ have an SCN1A missense mutation and not a truncating one [4,5]. In Dravet syndrome, truncating mutations are associated with harder phenotypes than missense mutations [6]. Almost all patients with Dravet syndrome suffer their initial seizure in the first year of life and a later hot high body temperature induces seizures. The SCN1A point mutation (c.4186 C>T) leads to a loss of neuronal voltage sodium-channel function. Truncating mutations of SCN1A aren'tt dominant negative, but result in pure haploinsufficiency. Further studies are required the treatment Dravet syndrome with ketogenic diet and Epiduolex[10,11].

P33 Prevalence of epilepsy in a Japanese elderly population; the Hisayama study

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The aim of the present study was to examine the prevalence and causes of adult epilepsy in a general Japanese population.

We examined a total of 3333 Japanese residents in the town of Hisayama aged ≥40 years in 2012-2013. The examination was performed mainly at the municipal center for health promotion, but some subjects were examined in their homes, hospitals, or nursing homes.

Twenty-three subjects had a diagnosis of epilepsy. The prevalence (95% confidence interval [CI]) of epilepsy per 1000 was 6.9 (4.1-9.7) in total, 4.9 (1.3-8.5) in men, and 8.4 (4.3-12.5) in women (P = 0.23 between sexes). The prevalence of epilepsy was significantly higher in the elderly (aged ≥65 years; 10.3 per 1000 [95% CI 5.4-15.1]) than in the middle-aged (aged 40-64 years; 3.6 per 1000 [95% CI 0.7-6.4]; P = 0.02). The major cause of epilepsy was cerebrovascular diseases (n = 11; 48% of the epilepsy patients). More than half of the epilepsy patients experienced the first episode of seizure in older age (≥65 years; n = 13; 57%). The findings of this study suggest the clinical importance of the prevention of cerebrovascular diseases to reduce the burden of epilepsy in the future.The aim of the present study was to examine the prevalence and causes of adult epilepsy in a general Japanese population. We examined a total of 3333 Japanese residents in the town of Hisayama aged ≥40 years in 2012-2013. The examination was performed mainly at the municipal center for health promotion, but some subjects were examined in their homes, hospitals, or nursing homes. Twenty-three subjects had a diagnosis of epilepsy. The prevalence (95% confidence interval [CI]) of epilepsy per 1000 was 6.9 (4.1-9.7) in total, 4.9 (1.3-8.5) in men, and 8.4 (4.3-12.5) in women (P = 0.23 between sexes). The prevalence of epilepsy was significantly higher in the elderly (aged ≥65 years; 10.3 per 1000 [95% CI 5.4-15.1]) than in the middle-aged (aged 40-64 years; 3.6 per 1000 [95% CI 0.7-6.4]; P = 0.02). The major cause of epilepsy was cerebrovascular diseases (n = 11; 48% of the epilepsy patients). More than half of the epilepsy patients experienced the first episode of seizure in older age (≥65 years; n = 13; 57%).

The findings of this study suggest the clinical importance of epilepsy in the elderly to reduce the burden of epilepsy in the aging society.

P34 Is intracranial electroencephalography useful for planning resective surgery in intractable epilepsy with ulegyria?

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Intractable epilepsy patients with ulegyria could be candidates of resective surgery. Complete resection of ulegyria in the epileptogenic hemisphere is associated with favorable seizure outcome. However, the strategy can be associated with post-operative functional deficits. We evaluated the extent of resection and postsurgical outcomes in epilepsy patients with ulegyria who underwent intracranial electroencephalography (iEEG) monitoring prior to resection in order to clarify the efficacy of partial resection of ulegyria guided by iEEG.

The consecutive epilepsy patients with ulegyria who underwent iEEG prior to resective surgery between 2011 and 2017 with a minimum follow-up of 12 months were reviewed. Ten patients were included in our study (7 males). The diagnosis of ulegyria was made on the typical pattern of cortical atrophy especially at the sulcal bottom on magnetic resonance imaging (MRI). IEEG study was indicated after comprehensive preoperative evaluations including high-field MRI, long-term video-EEG, magnetoencephalography, and F18-fluorodeoxyglucose-positron emission tomography. The planning of resection was on the basis of iEEG analysis.

The median age at surgery was 12.5 years (7-34), median duration of follow-up was 23.5 months (12-72). Ulegyria was located at the occipital lobe in 3, parieto-occipital region in 4, fronto-parieto-occipital region in one, parietal lobe in one, and fronto-temporal region in one patient. Five patients had bilateral lesions. Epileptic focus was localized in the unilateral hemisphere and intracranial electrodes were implanted unilaterally in 9 cases. In the remaining one case with bilateral lesions, electrodes were implanted bilaterally. The extent of MRI lesion was covered by the electrodes in all cases. Seizure onset zones (SOZ) and irritative zones (IZ) were identified in all cases, and were completely resected in 7 cases. In the remaining 3 cases, the SOZ and IZ were only partially removed because the eloquent cortices and the epileptogenic zones overlapped. Ulegyria of the epileptogenic side was totally resected only in one patient. Seizure freedom was achieved in 4 patients, including 3 after partial lesionectomy. Visual field deficit was seen in 4 patients.

Although seizure outcome after partial lesionectomy is limited, iEEG-guided partial lesionectomy provides reasonable chance of post-operative seizure freedom with lower risk of functional deficits.

P35 The brain network research of stereoelectroencephalography guided radiofrequency thermocoagulation (SEEG-guided RFTC) for treatment in the temporal lobe epilepsy

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SEEG-guided RFTC for treatment in epilepsy has been increasingly popular since it firstly underwent in Lyon. As to its mechanism, three hypotheses were put forward. One was that thermocoagulation maybe lesion the neuron, wipe out the abnormal discharge; one was that thermocoagulation maybe lesion the nerve fibers and block the propagation of abnormal discharge; another was that thermocoagulation maybe change the topological attributes of the brain network, and further change the brain function. Up to now, we have completed three parts of study about the hypothesis. The first part was some experiments, which included RFTC experiments on egg white, isolated human brain, and the RFTC observational experiment on pork, living human brain. Some appropriate RFTC parameters and technical key points were concluded. It turned out that the volume of RFTC lesion was related to RF power and duration. The stronger the power was, and the longer the duration was, the larger the volume would be within a certain range. The second part was clinical research, which summarized some seizure frequency before and after RFTC, determined the optimal indication, contraindication and technical parameter. The effect following-up was smoothly completed. The third part was mechanism research. The RFTC mechanism was deeply investigated from three angles of diffusion tensor imaging (DTI), brain structural and functional network. DTI research found that there was fractional anisotropy (FA) decrease and mean diffusion (MD) increasement in epileptics compared with normal subjects. All fibers through the RFTC targets nearly droped off, which further deduced that the brain network consisted of the gray matter and white matter possibly altered. As we all know, epilepsy is a kind of network disease. To explore the change of the brain network attributes before and after SEEG-guided RFTC, we further did the following clinical research.

6 patients with the right temporal lobe epilepsy underwent SEEG-guided RFTC. PANDA software toolkit was used to process DTI data before and after RFTC, during which 246 and 90 brain regions template were applied respectively to construct brain structural network. Then Gretna software toolkit was utilized to network analysis based on graph theory. The network attributes of all brain regions before and after RFTC were further assessed by Paired-Sample T test, and there would be significant difference if $p< 0.05$. All patients have been followed up for at least 27 months.

5 of 6 cases improved by over 50% decrease in epilepsy frequency, and especially one patient got 34 months of seizure freedom after RFTC. There was no global network metrics change. Whether 246 regions binary network or 90 regions weighed network, there was a significant difference ($p< 0.01$) on the local attributes of the brain network nodes before and after RFTC, and most of these nodes focused on the right temporal lobe. A majority of network attribute change were consistent, for example, the value of nodes degree, betweenness centrality, and local efficiency all went down on the temporal middle gyrus.

SEEG-guided RFTC can treat the temporal lobe epilepsy through altering the attributes of brain network. Brain network research may contribute to localize the epileptogenic zone.

P36 Interictal magnetoencephalography in parietal lobe epilepsy – comparison of equivalent current dipole and beamformer (SAMepi) analysis

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Patients with parietal lobe epilepsy (PLE) are less frequent in epilepsy surgery series than patients with frontal or temporal lobe epilepsy. Magnetoencephalography (MEG) is often used in the preoperative assessment for epilepsy surgery. There are no previous reports investigating the use of MEG specifically in patients with parietal lobe epilepsy. We compared three different analysis methods to localize the sources of interictal epileptiform MEG activity in PLE patients.

We analyzed the preoperative interictal MEG of 17 operated PLE patients. Three source analysis methods were utilized: (1) equivalent current dipole (ECD) analysis with a spherical conductor model; (2) ECD with a boundary element method (BEM) conductor model; and (3) SAMepi - a novel kurtosis beamformer method. Localization results were compared between the three methods, to the location of the resection and to the clinical outcome.

Fourteen patients showed epileptiform activity in visual analysis. Unifocal concordant (compared to resection) ECD localization to the posterior quadrant was seen in nine patients in the analysis with a spherical conductor and eight patients in the BEM analysis. One patient showed a false unifocal frontal midline localization with both conductor models. Eleven patients showed an epileptiform finding in SAMepi: six patients had a unifocal concordant quadrant localization, while one patient showed an ipsilateral frontal localization. A unifocal finding in both the visual/ECD and in the SAMepi analysis was associated with a greater chance of seizure-freedom ($p=0.02$). There was no significant difference in the distances from the unifocal MEG localizations to the nearest border of the resection with either the BEM ECD analysis or the SAMepi analysis compared to the ECD analysis with a spherical conductor model.

A unifocal finding in both the visual/ECD and the SAMepi analysis was associated with good clinical outcome. Neither the ECD analysis with a BEM conductor model nor the SAMepi analysis showed significantly more concordant (compared to resection) localization results than the ECD analysis with a spherical conductor model.

P37 ROSA rehearsal: using 3D printing technology to facilitate the introduction of stereotactic robotic neurosurgical equipment

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The use of frameless stereotactic robotic technology has rapidly expanded since the FDA approval of the Robotic Surgical Assistant (ROSA) in 2012. While the safety and accuracy of the ROSA platform has been well-established, the introduction of complex robotic technology into an existing surgical practice poses technical and logistical challenges particular to a given institution. In the nine years since the ROSA gained FDA approval, numerous reports of its safety and accuracy have appeared in the literature. While the ROSA system has undeniably advanced neurosurgical practice, its introduction into an operative environment presents typical challenges associated with the introduction of any new technology. These include work-flow related logistics, such as patient positioning relative to the new equipment; optimal placement of the machine itself with respect to the surgical scrub technician and operating surgeon; considerations of limitations in the reach of the robotic arm; and patient-safety challenges, such as maintaining sterility, decreasing operative/intubation time, and minimizing surgical error. We describe the use of a 3D printed patient model for presurgical positioning and trajectory optimization for SEEG in pediatric patients. Our hope was to better facilitate the integration of new surgical equipment into the armamentarium of a well established pediatric neurosurgery practice.

The patient's external soft tissue features and bone were segmented from the stereotactic MRI and CTA. In a preoperative rehearsal session, which included neurosurgical attendings, residents, and surgical auxiliary staff, the patient model was pinned and registered using the ROSA platform, and SEEG was performed. The entire dry run of the procedure was performed prior to actual operative day.

Utilization of the 3D-printed model enabled optimization of patient pinning and positioning on the ROSA and increased staff familiarity with the logistics of the robotic technology. SEEG successfully avoided collisions and confirmed appropriate robotic arm positions on the 3D printed model. These rehearsal maneuvers decreased operative and intubation time for the patient and improved operative staff familiarity with the robotic setup. It greatly decreased operative stress and anxiety for the entire operative team.

Use of a 3D-printed patient model enabled more accurate preoperative patient positioning and trajectory planning in a pediatric patient. The ROSA rehearsal decreased operative time and increased our working familiarity with a new piece of complex surgical equipment prior to any child stepping into the operating room.

P38 Neuropathological and genetic alterations in hemimegalencephaly and polymicrogyria

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Progress in molecular genetics lead to the detection of various mutations associated with hemimegalencephaly (HME) and polymicrogyria (PMG). In epilepsy surgical sections from HME and PMG patients, abnormal architecture of both, white matter and cortical layering have been shown. However, both the impact of postnatal brain plasticity and the role of the mutations found are still unclear. We focused on the neurite outgrowth inhibitor A (NogoA), a factor that has been shown to be upregulated in Tuberous Sclerosis Complex (TSC) and Focal Cortical Dysplasia IIB (FCD IIB) brain lesions. Characterization of the lesional distribution of NogoA in HME and PMG could enable a better understanding of the pathobiology of genetic epilepsies.

We analyzed epilepsy surgery specimen from 15 patients with HME and/or PMG, and compared them with those from patients with Mild Malformations of Cortical Development (MMCDs; n= 6), FCD IIB (n=22) and TSC (n=8). As control group we used normal brain tissue of autopsy and biopsy cases (n=15). Immunohistochemistry was used to characterize the cellular expression of NogoA. Slides were digitalized and the overall positive immunoreactivity was automatically evaluated with an ImageJ based macro. Next Generation Sequencing (Ion AmpliSeq Neurology Panel) was also performed using saliva and/or blood samples of HME, PMG, FCD IIB and TSC patients.

Mutations associated with epilepsy, were found in 75% of our HME and PMG cases, including genes involved in mTOR signaling (25% PIK3CA and 12,5% NPRL3). Immunohistochemical data showed a significantly increased expression of NogoA in the HME and PMG group, compared to controls. We also found a significant upregulation of NogoA in Focal Cortical Dysplasia IIB, whereas other malformations of cortical development like MMCDs or TSC (may be due to the small sample size) did not show significantly altered NogoA expression.

The presence of NogoA in epileptogenic lesions of HME, PMG and FCD IIB could inhibit potential regeneration and may have a negative impact on brain plasticity. Further studies are needed to evaluate how the different mutations are associated with this alteration.

P39 Early recovery of interhemispheric Functional connectivity of Corpus Callosotomy

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To investigate whether the interhemispheric functional connectivity (FC) recovers in the first year after total callosotomy.

Eight epilepsy patients undergoing total callosotomy were recruited. Resting-state functional MRI were acquired before and after surgery. The precallosotomy and postcallosotomy interhemispheric and intrahemispheric FC were analyzed by using graph theory and voxel-mirrored homotopic connectivity (VMHC). The seizure outcome was scored using the Engel surgical outcome scale.

After callosotomy (mean postoperative interval: 4 months), the network density, the average node degree, the characteristic path length and global efficiency of the whole interhemispheric networks were significantly decreased, compared to those in the precallosotomy networks. However, postcallosotomy interhemispheric FC and homotopic VMHC were not significantly reduced in bilateral frontal and temporal lobes. The network density, and average node degree of the intrahemispheric networks are significantly increased. The global efficiency of intrahemispheric networks is unchanged.

The interhemispheric FC may be preserved or recover early within the first postoperative year after total callosotomy, particularly in the frontal and anterior temporal lobes.

P40 Common MRI and Genetic Factors to Predict Lennox-Gastaut Syndrome

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Lennox-Gastaut Syndrome (LGS) is a severe form of epilepsy with numerous etiologies that affects 2-5% of children with epilepsy. The diagnosis of LGS is made in patients with cognitive impairment, multiple seizure types (tonic, atonic, and atypical absence in particular) and specific EEG findings of slow spike wave complexes (<2.5 Hz) and paroxysmal fast activity. Often the diagnosis is delayed since the EEG abnormalities are not constantly present. The goal of this study was to see if there are specific genetic findings, imaging abnormalities or a prior diagnosis that could predict the evolution to LGS in an earlier stage of disease.

This study is an IRB approved retrospective chart review done at a single tertiary care pediatric epilepsy center that included patients diagnosed with LGS between 2010 and 2018. Data collected included genetic testing results, MRI imaging and other diagnoses prior to confirmed LGS diagnosis.

95 participants were identified. Of all genetic testing reviewed, 14 participants had a chromosomal abnormality, 18 had a monogenetic defect, 26 had no genetic abnormality found and in 37 participants genetic testing was not done. MRI findings: 21 participants had ventriculomegaly or cortical volume loss, 21 had a cortical malformation, 18 had evidence of ischemia, 18 participants had some other finding on MRI, 14 had no abnormalities and 2 participants had no MRI results available. When reviewing the participant's prior diagnoses, we found that 38 patients had infantile spasms, 7 had hypoxic-ischemic encephalopathy (HIE), 37 had other prior syndromes, 10 had unknown medical history and 3 participants had no prior diagnoses or syndromes.

A majority of the participants reviewed had infantile spasms before receiving an LGS diagnosis. Many other participants also had identifiable etiology from MRI imaging or clinical history including perinatal stroke or HIE. Cortical malformations and ventriculomegaly or cortical volume loss were the predominant findings on MRI, followed by evidence of ischemia. As far as genetic testing, we were not able to determine any specific finding linked to the LGS diagnosis as a majority of the participants did not have genetic testing done or had no genetic abnormality identified. Overall this study confirms that participants presenting with infantile spasms, perinatal stroke, and HIE could acquire LGS in the future. Further analysis of this data could provide good predictive tools for clinicians treating patients with infantile spasms and other neonatal/infantile brain disorders. This could lead to an earlier stage diagnosis of LGS and better medical treatment and management of the disease which could improve their seizure control and quality of life.

P41 Subcortical Band Heterotopia by DCX gen mutation: One male and one female

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Subcortical band heterotopia (SHB) also known as a double cortex syndrome, is an abnormal cell migration disorder characterized by ribbons of grey matter within the central white matter between the cortex and the ventricular surface. Affected patients, who normally are females, present an epilepsy with different types of seizures which will be farmacoresistant and different degrees of intellectual disability. Clinical spectrum is similar in both sexes. In MRI, males had frequently partial SHB, diffuse SHB with posterior predominance and pachygiria-SBH. Classical diffuse SHB and diffuse with anterior predominance, are more frequent in females. Mutation in the gene encoding doublecortin (DCX), is responsible mainly of two migration disorders: Classic lissencephaly (usually in males) and Subcortical band heterotopia (usually in females, rarely in males)

This is a retrospective study of the Hospital del Mar, Barcelona. We reviewed the paediatric neurology database looking for Subcortical Band Heterotopia and we found two patients: One female and one boy Cranial MRIs were reviewed for the same neuroradiologists. Routine scalp video-EEGs were preformed on both patients and a prolonged video-EEG recording for presurgical evaluation was done for the girl. Blood samples for DNA were obtained with informed consent. Mutation detection was preformed by single gene testing with the girl and by multigene panel with the boy

Case 1. 16 years old girl with focal motor epilepsy starting five years ago. Her aunt had epilepsy during infancy. Born at term without problems in perinatal period. Normal motor development. Moderate intellectual disability (Weshler test: 46) and behaviour disturbance in treatment with Quetiapine. Diffuse Subcortical Band Heterotopia with mild posterior predominance. Heterozigotic for the novo DCX mutation. Because of farmacoresistant epilepsy she had a presurgical evaluation that showed a bifrontal epilepsy. We offered vagal nerve stimulation. Finally, adding Perampanel (plus Valproate and Levetiracetam) she' s seizure free for the last 11 months. Case 2. 15 years old boy with focal motor epilepsy who started one year ago. No family history of seizures or epilepsy. Born at term without abnormal events in perinatal period. Normal psychomotor development. He has a mild learning disability. MRI: diffuse Subcortical Band Heterotopia with posterior predominance . EEG: Temporo-parietal interictal discharges. High-resolution karyotypin was normal. Multigene panel: Nonsense mutation in DCX gen in mosaicism. Both parents were sequenced too. Treated in monotherapy with Levetiracetam. He's seizure free since the beginning of the treatment (now 17 years old).

Subcortical Band Heterotopia by mutation in DCX gene, is an abnormal cell migration disorder which occurs more frequent in females but is rare in males. In contrast to literature we show the clinical variability between sexes. Moreover we describe a male, rarely presenting SBH and additionally with good evolution of his epilepsy and without intellectual disability. Like in the literature our male presents a diffuse SHB with posterior predominance.

P43 The effect of different colors and white light on bioelectrical brain activity in adults with photosensitive generalized epilepsy

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Photosensitive epilepsy (PSE) is the most common form of reflex epilepsy, affecting up to 10% of children with epilepsy. It is thought, that 4 to 9% of the population carries this risk factor, and people may be unaware of this risk. Despite the high prevalence of this disorder, little is known about the mechanisms of human PSE. Considering that the role of colour in photosensitive epilepsy (PSE) remains unclear, we designed a study to determine the potential of different colours and white light to trigger photoparoxysmal responses (PPRs) under stringent controlled conditions in adults with photosensitive generalized epilepsy.

After assessing their photosensitivity to stroboscopic white light, we studied 45 consecutive PSE patients (mean age 30.1±8.2 years, 34 women), using a specially designed colour stimulator. Stimuli included: pulse trains between 10 and 60 Hz of white light and of all primary colours, and also isoluminant alternating time-sequences of colours. For the statistical analysis MS Excel, SPSS v. 23 sowtware packages were used, applying mixed model method.

Whereas all the 43 patients were found to be sensitive during the strobo- scopic and pattern protocol, only 11 showed PPRs at least in one session when studied with the colour stimulator. Yellow and red-coloured stimuli elicited PPRs in all these patients, whereas blue and violet-colored light did so only in 7 and 8 patients accordingly. Polyspikes were registered in 1, spike and wave complexes in 4, polyspike and wave complexes - in 7 patients. The mean duration of responses was 1.38s (yellow), 1.85s (red), 0.52s (blue), 1.03s (violet). The reduction of ED duration was statistically significant ($p<0,05$) with blue colour filter in comparison with white colour, but we did not find any statistically significant ED change using yellow ($p=0.97$), violet ($p=0.15$) or red ($p=0.11$) colour filters.

Our results suggest that the prescription of spectacles with blue-coloured lenses, tailored to the patient, can be an effective preventative measure against visually induced seizures.

P44 Pediatric epilepsy surgery in Rolandic Focal Cortical Dysplasia Type 2

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Epilepsy surgery in the rolandic cortex presents a difficult problem to deal with, due to the assumption of unacceptable postsurgical neurological deficit in primary motor and sensory areas. We carried out a review of epilepsy surgery approaches and results in children and adolescents with FCD type 2 involving the rolandic cortex (FCD2-RC).

Out of a total of 98 patients with MRI-suspected FCD type 2 studied between 2008 and 2018, we selected 22 cases (22%, 11 females) diagnosed as having FCD2-RC; 14 of whom were operated-on. Presurgical and surgical strategies were supported by functional neuroimaging (fMRI, DTI Tractography) and invasive neurophysiological techniques (extraoperative in 13, intraoperative in 10), including different combinations of intracraneal EEG (depth plus subdural electrodes in 10, just depth electrodes in 4), electrical cortical stimulation, somatosensory evoked potentials, motor evoked potentials and subcortical white matter electrical stimulation.

The electro-clinical profiles were highly suspicious of FCD2-RC in all patients, even in 6 referred as "MRI-negative". Median age at seizure onset was 15 months (range 1 month-17 years). Most cases described periods with highly refractory seizures and polytherapy and had experienced focal status epilepticus (including Epilepsia Partialis Continua in 4), linked to a decline in motor and/or cognitive performances. Distinctive interictal scalp EEG findings included focal rhythmic slow activity and spikes and low voltage fast spiky activity. Detailed 3T MRI and FDG-PET/MRI co-registration showed subtle or mild findings suggesting FCD in 6 cases, affecting predominantly the bottom of the central or precentral sulcus, and well-defined lesions in 16. Abnormal cortex involved the precentral gyrus in 11, the postcentral gyrus in 6, and both precentral and postcentral gyrus in 5. In 10 patients FCD2-RC was located in the left hemisphere, 7 of whom were left-handed. Integration of neurophysiological and functional neuroimaging evaluations turned out to be crucial for the identification of the epileptogenic and functional cortex in all cases, despite limitations of certain techniques in some instances, such as in small children or in those with continuous seizures.Thirteen out of 14 patients were seizure free at last postsurgical follow-up (mean 2,8 years, range 7 months-7 years). Two cases experienced early postsurgical seizure aggravation, and 2 children underwent a re-intervention. Antiepileptic drugs were successfully tapered after surgery in the great majority of cases, despite minor postsurgical EEG changes being common. Seven cases experienced a predicted immediate postsurgical motor deficit, which improved significantly over time, reaching good functional motor performance in all except one. None complained about somatosensory deficit. Neuropsychological and/or academic and social performances improved in all operated-on cases with seizure control and antiepileptic drugs reduction.

Epilepsy surgery may constitute the best treatment option in pediatric patients with drug-refractory epilepsy due to FCD2-RC. Integrative multimodal evaluation and intraoperative neurophysiological monitoring ensure tailored resections and optimize prediction and control of surgical neurological risk on an individual basis. Postsurgical functional motor deficits may be avoided, may be transitory, or much better tolerated than previously expected and compensated by an improvement in neuropsychological prognosis.

P45 A phase 1b/2a study of TAK-935 (OV935) as adjunctive therapy in patients with developmental and epileptic encephalopathies (DEE)

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TAK-935 (OV935) is an inhibitor of cholesterol 24-hydroxylase that converts neuronal cholesterol to 24S-hydroxycholesterol (24HC). 24HC is a positive allosteric modulator of glutamatergic NMDA receptors. 24HC may also regulate glial function, including potassium homeostasis and inflammation.

This phase 1b/2a trial examined TAK-935 in adult patients with developmental and epileptic encephalopathies (DEE). Patients were randomized to a double-blind placebo-controlled phase (30 days; target dose 300 mg BID); and an open-label phase (60 days). Primary endpoints were safety and tolerability. Exploratory endpoints were 24HC plasma levels and change in seizure frequency.

Eighteen patients were randomized (mean age 29 years, range 19-45, male n=14) with heterogeneous types of DEE. 14/18 (78%) patients completed the study; four withdrawals occurred (two in each phase). During the open-label period, 11 patients (68.8%) experienced a treatment-emergent adverse event (TEAE). The majority of TEAEs were mild. Five serious TEAEs, all seizure cluster related, were reported among three subjects receiving TAK-935. ITT analysis in the open-label phase of all 16 patients receiving at least one dose of TAK-935 showed a 36% median reduction in seizure frequency from baseline to Day 85 (end of maintenance). Three patients on perampanel had increases in seizure frequency potentially related to a pharmacodynamic interaction, supported by preclinical data on AMPA/NMDA. A post-hoc analysis of the median seizure reduction in the last 28 days on TAK-935 using the actual last day of treatment including taper was 46% (n=14) and 61% (n=11), excluding patients on perampanel and using the scheduled last visit day (Day 92). Two patients (12.5%) became seizure free in the last four weeks of treatment. Mean 24HC levels decreased 71% from baseline to Day 85 (n=10), representing a potential biomarker of target engagement.

TAK-935 was well tolerated with initial evidence of possible efficacy, and demonstration of a promising biomarker.

P46 Valproate use among female patients in Lithuania: a time-series analysis

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Two separate regulatory recommendations discouraging valproate use in girls and women aged from 0 to 49 years were published in both 2014 and 2018 after the European Medicines Agency (EMA) finished ongoing valproate referral procedures. The latter were based on an increased realization of the fetal risks posed by valproate and the need to minimize exposure to the drug for women of reproductive age. The most recent regulatory restrictions include recommendations not to prescribe valproate for pregnant patients and female patients of childbearing age, or carry out a pregnancy prevention programme otherwise. We evaluated, whether the absolute number of female patients using valproate decreased (in relation to the pre-intervention secular trend) in Lithuania under the influence of these restrictions.

An interrupted time series (ITS) analysis with a non-seasonal autoregressive integrated moving average (ARIMA) model adjusted for first-order autocorrelation was performed with the intention to detect changes in secular trend or changes in level around an intervention point, when the outcome was perceived to be the number of female patients using valproate. This method allows detecting the impact of a distinct intervention at the population level, although not proving causation. Patient reimbursement data for valproate was extracted from the National Health Register Fund of Lithuania for the period between 2013 and 2018.

After the referral procedure of 2014, the only decrease in patient number was noted in the group of female patients under 15: the difference between pre- and post-intervention slopes was -4.83, 95% CI = -9.45 to -0.22, P = 0.041 and the change in level was statistically significant after 15 months post-intervention (-40.06, 95% CI -79.26 to -0.86, P = 0.046) with a peak after 21 months (-49.72, 95% CI = -96.94 to -2.51, P = 0.04). The intervention in the first half of 2018 had a significant effect for women of reproductive age (15-49 years) and older. A significant level effect was noted 3 months post-intervention (-201.28, 95% CI = -310.61 to -91.96, P = 0.001 and -170.60, 95% CI = -287.73 to -53.48], P = 0.007 for the two age groups, respectively). The effect lasted during subsequent months and peaked at 9 months post-intervention (-268.46, 95% CI = -393.04, -143.87, P < 0.001 and -315.16, 95% CI = -465.41 to -164.90 , P < 0.001, respectively)

The data shows a decrease in absolute female patient number using valproate after the most recent EMA regulatory restriction in the first half of 2018, when considering female patients of reproductive age and older. The effectiveness of the earlier intervention in 2014 could be questioned as the only decrease in relation to the secular trend was in the number of female patients under 15. Such results relate well to the position and findings published by the French Agency for the Safety of Health Products (France ANSM) early in 2017, when no significant effect for prescription patterns was observed after the 2014 EMA warning and more data and concerns emerged in relation to valproate use among female patients of reproductive age. Our research is limited by being retrospective and non-inclusive for demographic, disease prevalence factors as well as not distinguishing among diagnoses for which valproate was prescribed. Future studies of local or international level would be necessary to evaluate the real impact of EMA regulations and suggest improvements for such refferal processes.

P47 SEEG evidence of subcortical structures participation to seizure developing in focal epilepsy

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Focal epilepsy has traditionally been considered as a cortical disease. Nevertheless Gastaut, already in the early '70ies, introduced the idea of focal epilepsy as a cortico-subcortical disease, in which the subcortical structure could be even responsible of the seizure starting. However, evidence from direct SEEG recordings from subcortical structures is scant and mainly limited to MTLE. The aim of this work is to evaluate the participation of subcortical structures in the epileptogenic network in a large series of patients.

Forty-eight patients who had at least an intracranial electrode implanted in the thalamus were studied. Twelve patients had also an electrode in the caudate nucleus and three patients in the putamen. One hundred and six seizures were visually analyzed and the epileptogenicity of the different brain regions was quantified by the means of the Epileptogenicity Index (EI). Particular attention was addressed on the neurophysiologic pattern of ictal discharge.

Twelve patients (18 seizures) presented EI > 0.3 in the thalamus in at least one seizure. Two patients presented EI values > 0.3 in the caudate nucleus and one patient in the putamen. To visual analysis thalamus participates in seizures in the great majority of patients (90% in the first 15 seconds). Different ictal patterns were observed: low voltage fast activity (42 %), rhythmic spikes (16%) or rhythmic theta (42%). High frequencies ictal discharges (> 128 Hz) were also observed in the thalamus in 13 patients. A significant correlation was found between extension of the epileptogenic network (% brain region with EI > 0.3) and epileptogenicity in the thalamus.

Thalamus could be early involved in seizure generation and the degree of his epileptogenicity (evaluated with EI) correlates with the epileptogenic network extension. Other subcortical structures, as caudate nucleus and putamen, could also be implicated.

P48 Neuroimaging findings as biomarkers of epilepsy risk and neurodevelopment at two years in patients with Tuberous Sclerosis Complex (TSC).

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In this study we aimed to 1) prospectively identify MRI biomarkers of epileptogenesis, at early age and before the onset of recurrent seizures and 2) correlate these MRI biomarkers with first years neurodevelopmental outcomes, in a large multicenter cohort of patients with TSC

Prospective and longitudinal data were collected in a prospective international multicentre project (EPISTOP). Ninety-seven patients with a definite diagnosis of TSC, were included before the age of four months and before seizure onset. MRI acquisition was harmonized across centers with predefined protocols. MRI characteristics (tubers, radial migration lines (RML), white matter abnormalities, cyst and calcifications) were visually evaluated, lesions were detected semi-automatically. Presence of TSC associated lesions and total lesion volumes were correlated with epilepsy characteristics and with neurodevelopmental outcome as assessed with Bayley Scales of Infant and Toddler Development at two years, using binary logistic or linear regression analysis. All volumes were corrected for total brain volume.

Higher ratios of tuber and total lesion volume over total brain volume were significantly correlated with younger age at first epileptiform EEG activity, the development of clinical seizures in the first two years of life, and to refractory epilepsy.
 Patients with presence of RML, and those with a higher RML/total brain volume ratio more often had clinical seizures and refractory epilepsy.
 Higher ratios of tuber and total lesion volume over total brain volume were related to lower cognitive and language indices. Higher radial migration line volume/ total brain ratios and presence of tubers were related to lower cognitive indices.

In children with TSC, there is a striking association between MRI characteristics visualised in the neonatal and early infantile brain, epilepsy characteristics, and neuropsychological outcome at two years. This finding will improve our care and guidance in infants with TSC

P49 Visual field deficits after temporal lobe surgery in epilepsy patients: comparison of anterotemporal and subtemporal approach

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Most operations in temporal lobe epilepsy (TLE) include the resection of the amygdala-hippocampus-complex (amygdalahippocampectomy, AHE) and are carried out as temporal pole resection with AHE (TPAHE), as anterior two-third temporal lobe resection (TLR) with AHE (2/3TLR) or as selective AHE (sAHE) over a posterior subtemporal approach (STAHE). The extent of resection is dependent on the suspected size of the temporal lobe lesion, judged on MRI. The indication for anterior TLR is growing, because improvements in MRI technology show more, probably irrelevant, abnormalities of the temporal lobe. Anterior TLR (TPAHE, 2/3TLR) bear the risk of postoperative visual field deficits (VFD) due to immediate vicinity of the Meyer´s loop of the visual tract anterior of the temporal horn of the ventricle. Some studies showed that STAHE has a lower rate of VFD, most likely because the approach is inferior of temporal horn and the visual tract. The purpose of this study is to show, whether the rate of VFD in STAHE is low and whether the use of navigated diffusion tensor imaging (DTI)-marked visual tract can reduce VFD in anterior TLR to the level of STAHE.

In 24 patients temporal lobe surgery was performed with navigation, based on preop DTI imaging of the visual tract. The extent of the volume of the visual tract was regulated over the BrainLab software by the surgeon. Pre- and 3 months postoperatively visual field diagnostic using Goldmann perimetry were performed.

Seventeen patients had anterior TLR with AHE (TPAHE, 2/3TLE), of those, 11 showed a VFD in the contralateral upper quadrant, 6 patients had no new VFD. Three patients had an anterior TLE for resection of an epileptogenic lesion without AHE, of those two had a VFD contralateral upper quadrant. Three patients had STAHE, none of them developed VFD. In single patient a temporal lesion within the visual tract was resected through a subtemporal approach, the patient developed a contralateral upper quadrant VFD. Most patients with detectable VFD did not experience a noticeable impairment.

In STAHE 1/4 of the patient showed VFD, in anterior TLR 3/4, despite the use of navigated DTI-marked visual tracts. Since MRIs show more abnormalities, the indication for anterior TLR is growing compared to STAHE, as might the number of patients with postoperative VFDs.

P50 Epileptic Spasms – Clinical and Neurophysiologic Profile

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Epileptic spasms (EE) are one of the most common seizures types in pediatric age and include a variety of electroclinical syndromes. The aim of this study is to analyse EE identifying electro-clinical, etiological and prognostic profile.

Descriptive and retrospective study, based on the review of the clinical processes of children with EE, between 1998 and 2018, at Hospital Pediátrico de Coimbra- Portugal. We analysed: gender, previous history, family history, age of onset, clinical semiology, psychomotor development, imaging, genetic and metabolic investigation, response to treatment, electroclinical syndrome and etiological diagnosis.

We studied 99 children, with no gender predominance. The age of onset of EE was between 15 days and 11 years old. Clinically, the EE in 52.8% (38/72) were symmetrical, in 33.3% (24/72) asymmetrical; 42.9% (42/98) in extension; 36.7% (36/98) in flexion and 20.4% (20/98) mixed. Eighty-three percent (82/99) associated another seizure type. The video-EEG identified hypsarrhythmia in 41.4% (41/99), focal / multifocal paroxysmal activity in 33.3% (33/99) and generalized paroxysmal activity in 11.1% (11/99). Only 10 children (10.4%) controlled spasms in monotherapy; and 68.75% (66/96) were drug resistant. The most commonly used antiepileptics were vigabatrin, 53.1% (51/96), valproate 20.8% (20/96) and phenobarbital 8.3% (8/96). Almost all (90.8% - 91/98) had neurodevelopment problems: developmental delay in 75.5% (74/98) and autism spectrum disorder in 11.2% (11/98). We identified an electroclinical syndrome in 70%: West 53.5%, Early Infantile Epileptic Encephalopathy 11% and Lennox-Gastaut 5%. Regarding the etiology, 33% were structural, 21% genetic; 13% multiple, 6% metabolic, 3% infectious and 23% unknown. Polymorphic seizures were associated with uncontrolled epilepsy at the last follow-up ($p = 0.002$). Drug resistance and specific etiology was associated with abnormal final psychomotor development ($p=0,037$ and $p=0,012$ respectively).

The epileptic spasms integrated mainly drug resistant epilepsies, with polymorphic seizures, associated with severe neurodevelopmental problems and in which the main etiology is structural.

P51 Giant Hypothalamic Hamartoma and Epileptic Encephalopathy Approach

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Hypothalamic hamartomas is a congenital, non-growing tumor which may be associated with gelastic seizures, focal or generalized seizures, as generalized epileptic encephalopathy and cognitive and behavior decline. The global outcome is usually related to neuro-surgical intervention.

We report a case of a grade VI giant hypothalamic hamartoma (Regis classification) diagnosed prenatal which associated from the age of 2 initially gelastic seizures, followed by focal seizures and precocius puberty. Seizures were drug resistant and associated cognitive regression and behavioural disturbances, concordant with the moment of frequent epileptiform discharges. The child has been operated at the age of 3 years 6 months with transcallosal anterior interforniceal approach. Considering the dimension of tumor, it has been done intraoperative EEG-monitoring during resection in order to see the moment of disconnection to the thalamic structures.

Almost 80% of the tumor has been resected without any complications. Despite the impressive resection and complete disconnection from hypotalamus and mammillary bodies, intraoperative EEG monitoring showed continous epileptiform discharges during the whole period of resection. 1 month and 1 year 6 months follow-up was seizure free, no epileptiform discharges on EEG, normal cognitive and behavioral development and precocious puberty.

Our case report demonstrates the efficacy of disconnection of a giant hypothalamic hamartoma from hypothalamus and mammillary bodies, despite the size of the tumor or the results of the intraoperative EEG monitoring.

P52 Efficacy of Perampanel in Electrical Status Epilepticus in Sleep in Children

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Perampanel is a unique anticonvulsant acting as a non-competitive AMPA receptor antagonist. The use of Perampanel in children with generalised epilepsies is limited and there is paucity of data available for its efficacy and safety in different paediatric epilepsy syndromes. Electrical status epilepticus during slow wave sleep (ESES) is a condition in which the epileptic patient starts to develop neurocognitive deterioration, any type of seizures and continuous electrical activity in the EEG during non-rapid eye movement (NREM) sleep. If left untreated it may lead to permanent neurocognitive deterioration. Thus, early diagnosis and treatment is essential in these children to preserve neurocognitive function

12-year-old boy had seizure onset at 9 years of age with EEG demonstrating generalised spike and wave discharges. He was commenced on Sodium Valproate and continued to have seizures despite dose escalation on monotherapy with sodium valproate. In addition, there was cognitive decline following onset of epilepsy. The overnight EEG recording demonstrated continuous spike and wave during sleep (CSWS). Patient was given a course of steroids with partial resolution of CSWS and some improvement in cognition. Patient developed weight gain and after weaning him off steroids he returned to his previous poor neuro-cognitive state. We report effect of Perampanel as an add on therapy

After commencing on Perampanel therapy with gradually escalating dose from 2 mg nocte to 6 mg nocte over a period of six weeks there was marked improvement in patient's cognitive ability, attention at school and day to day activities at home. Perampanel was tolerated well without any reported adverse effects. The sleep markedly improved and patient was reported to be refreshed in the mornings. There were no breakthrough seizures. The repeat overnight EEG demonstrated complete resolution of ESES with return of sleep background. EEG and other data will be shown in the presentation.

This case report highlights potential use of Perampanel for ESES in paediatric age group. A prospective study for this cohort of patients will be helpful in analysing its efficacy and safety for this indication. To our knowledge this is the first paediatric case report demonstrating complete resolution of ESES with Perampanel therapy.

P53 Educational project dedicated to schoolteachers for the correct management of epileptic seizures in school-age children

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Objective: Educate the school staff to correctly handle epileptic crises increasing the safety of young people at school and promoting the administration of emergency drugs. All this with the aim of reducing resorts to the first aid departments and the distance between hospital and territory.

Two-hour training meetings with school staff dedicated to illustrating the illness and the correct handling of seizures. During meetings two questionnaires will be distributed: one ex ante for information on epilepsy, willingness to administer the drug and anxiety in facing crisis; and one ex post to control the knowledge acquired. After a year, we interviewed the trained teachers to ask them if and how they handled seizures in the school environment.

740 questionnaires were distributed between January 2016 and November 2018. From the analysis an increase in knowledge of correct behavior to be taken during an epileptic crisis, a reduction in anxiety (average 3.6, average post 2.9, on a scale from 0 to 5) and an increase in willingness to administer drug emerged (from 54% to 89%). From interviews 17 seizure emerged and in 4 cases the drug is administered. In 4 cases teachers called ambulance and in 2 the child was admitted.

It can be asserted that the training course is efficient to improve knowledge of epilepsy and the handling of seizures with an increased willingness of school staff to handle the illness. We have a reduction in calls to the emergency health number (4/17) and in hospital admissions (2/17).

P54 Focused Ultrasound Treatment for Medically Intractable Epilepsy

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FUS treatment for intractable epilepsy including left mesial temporal lobe epilepsy (2 cases), hypothalamic hamartoma (2 cases), and left parieto-occipital MRI positive epilepsy (2 cases) has been done in recent three years. in our institute.

For TLE, subiculum was sonicated in one patient and postoperative result is satisfactory (Engel' s class IA) with postoperative follow-up two years and seven months, and for hypothalamic hamartomas the interface between hypothalamus and hamartoma was the target for two patients, postoperative seizure control is IIA(follow-up for 1y8ms) for one patient and IA(follow-up period 4ms) for another and left central lateral nucleus of the thalamus was the target for two patients of the left parieto-occipital epilepsy with Engel's Class IIB for both patients with follow-up period of eight months. The age of the patients ranged from 20years to 45 years with sufficient long duration of epileptic history. One left temporal lobe epilepsy has been just sonicated at the end of Februrary 2019, so that, any definite conclusion can not obtained at this time.

No adverse events have been observed for these 6 patients. Good success for hypothalamic hamartomas.

FUS treatment is a noninvasive new treatment for intractable epilepsy with some effect for some type of epilepsy such as, hypothalamic hamartoma, temporal lobe epilepsy, and inoperable MR positive lesional epilepsy such as left parieto-occipital lobe epilepsy. Skull density ratio (SDR) is one of the limiting factors to obtain a sufficient temperature to make a successful target lesioning, especially for Asian people. Further clinical esxperiences, long-term follow-up , and improvement of technical problems should be mandatory to obtain a final conclusion of the efficacy of MR-guided focused ultrasound treatment for medically intractable epielpsy.

P55 Ictal miosis – a rare symptomatology of simple focal autonomic seizures.

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Epileptic seizures, manifesting by pupils' size alteration, without impairment of consiousness, may remain unnoticed or may be mistaken with other nonepileptic events. There is a lack of comprehensive descriptions and evidence in the literature, regarding seizures with pupillary autonomic manifestation, proceeding as the isolated phenomena. This fact indicates the need of reporting the cases of focal seizures without impaired awarensess, clinically manifesting with pupillary changes, which should be discussed in order to remain aware of this rare seizure symptomatology and asses the actual frequency of them in a longer perspective.

We present a history, clinical and diagnostic implications regarding a 3,5-year-old boy, diagnosed with.focal seizures without impaired awarensess with autonomic manifestation

There were no pregnancy and delivery complications, also the psychomotor development was normal. Interictal EEG revealed sharp waves in occipital and parieto-occipital regions, pronounced over the right hemisphere. MRI of the brain was normal. Hospital observation and video recording confirmed focal seizures without impaired awareness with autonomic manifestation. He was successfully treated with carbamazepine and remains seizure free.

Our findings provide the evidence that focal epileptic seizures without impaired awareness may be elusive and difficult to recognize. Capturing the seizures on video monitoring may be essential to the diagnosis. Careful observation, proper diagnosis and early implementation of antiepileptic therapy may provide satisfactory and longlasting improvement in managing the seizures

P56 Multiple Radiofrequency thermocoagulation (RF-TC) for polymicrogyriawith startle seizure: case report

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A rare caseof polymicrogyria combined with startle seizure, havingreceivedstereo-electroencephalography(SEEG) for the detailed identification of the epileptogenic zone (EZ), is presented in this study.Sincethe functional areas in the patients' polymicrogyria were still retained, multiple SEEG-guided RF-TC were usedinstead of lesion resection. Finally, the patient reached Engel class IIa for a follow-up period of one year. There were no startle seizures, and important functional areas were protected.

The patient received a comprehensiveevaluation, including the detailed clinical historyand neurologic examination, neuropsychological testing,routine MRI, VEEG, PET, and Functional magnetic resonance imaging(fMRI) .We decided to proceed with SEEG to identify the EZand better define a possible resection range. According to theintracranial electrode results, the seizure onsetwasextensive, with cingulate sulcus and insular polestarted earlier than other electrodes.The fMRI results and intracranial electrical stimulation results suggest thatthe functional areas in the patients' polymicrogyria remained,multiple SEEG-guided radiofrequency thermocoagulation(RF-TC) was used, and a time window for efficacy observation was added. RF-TC was first applied in the cingulatesulcus and insular pole, and it rendered the patient free of startle seizures after two weeks of observation. Subsequently, RF-TC was usedfor thesecondly involved regions.

PostRF-TC outcome was evaluated at 3,6 months and 1 year later, the patient's startle seizure completely disappeared, and surgical outcome metEngel class IIa. Nosevere permanent neurological morbidity or cognitive impairment occurred afterRF-TC

Multiple SEEG-guided RF-TC should be used fordrug-resistant epileptic patients suffering from extensive malformation of cortical development with the function retained. This procedure has servedas a first therapeutic step before surgery or as a palliative treatment when surgery was not possible.

ANTISEIZURE DRUGS: LESSONS FROM THE PAST AND THEIR FUTURE

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The introduction of 20 second-generation antiepileptic drugs (AEDs) in the last three decades has improved patients' outcomes only to a limited extent. Several newer drugs offer tolerability advantages, including lower teratogenic risks, and lesser potential for drug-drug interaction. Facilitated drug development pathways for medicines targeting orphan indications have also broadened the pharmacological armamentarium for the treatment of rare epilepsy syndromes of infancy and childhood, including West syndrome, Dravet syndrome and Lennox-Gastaut syndrome. Despite these advances, however, second generation agents brought little or no incremental value in antiseizure efficacy, and the burden of drug resistance, particularly in epileptic encephalopathies, has not changed substantially over the years. The modest impact of newer AEDs on seizure outcomes can be explained by a combination of at least three factors, (i) the existence of major gaps in our understanding of the mechanisms of epileptogenesis, which prevents truly rational drug development; (iii) a trend to invest resources into development of structural derivatives of existing agents, mostly aiming at improving pharmacokinetic and tolerability profiles rather than intrinsic efficacy; and (ii) persisting utilization of preclinical models which prioritize discovery of symptomatic treatments, i.e. treatments that target seizures rather than the underlying cause of the epilepsies.

The old paradigms of drug discovery, however, are being changed, thanks to advances in pathophysiological knowledge, improved understanding of the mechanisms of drug resistance, and development of new in vitro and in vivo models (including models applicable to throughput screening) which reproduce the molecular defects responsible for epileptogenesis in individual patients. Examples of these innovative approaches include precision medicines for epilepsies caused by gain-of-function or loss-of-function of specific gene products, or the development of treatments targeting autoimmune or neuroinflammatory mechanisms. These paradigms require not only changes in drug discovery strategies, but also novel pharmacoeconomic models accounting for the fact that some highly effective precision treatments are likely to benefit only small subgroups of patients. Strategies to reduce development costs include more focused pathways for drug discovery and testing, innovative clinical trial designs with small sample sizes, and exploiting opportunities offered by repurposing of medicines already approved for other indications.

CASE REPORT: MRI-NEGATIVE FRONTAL LOBE EPILEPSY WITH HYPERKINETIC SEIZURE SEMIOLOGY AND INTERICTAL PSYCHOBEHAVIORAL CHANGE

Dr Aileen McGonigal

I will present the case of a young male patient with MRI-negative focal pharmacoresistant epilepsy, who underwent stereoelectroencephalographic (SEEG) exploration. He presented predominantly nocturnal seizures with hyperkinetic behavior. A characteristic feature of his case was interictal psychiatric disturbance with impulsive behavior and hyperphagia. Electroclinical features will be discussed in the context of the spectrum of frontal lobe seizure semiology. I will also discuss possible ictal/interictal interactions within prefrontal systems, related to altered interictal behavioral control in his case. Rasmussen encephalitis (RE) is a sporadic, progressive, inflammatory disorder mainly of childhood, associated with unihemispheric atrophy, severe focal epilepsy, intellectual decline, and hemiparesis. Neuropathologic features described in the surgical specimens show characteristics of chronic lymphocytic inflammation, microglial nodules, astrocytosis, and neuronal degeneration.

In 2005, a European group proposed formal diagnostic criteria. A group from the US review and amended them in 2013. With increasing experience and the use of these criteria, RE has become easier to recognize and to diagnose. Nevertheless, this disease remains rare, affects mostly children, sometimes adolescents and young adults and rarely older adults. Females are more often affected compared to males (3:2). No geographical or ethnic predominance has been noted so far. Typically, the disease starts in healthy children between 1 and 13 years (median, 7 years) with the majority developing seizures before the age of 10 years. Early seizures are often polymorphic with variable semiology, but motor manifestations are almost always reported. Other variable semiology of seizures with somatosensory, autonomic, visual, and psychic features has been described. The seizures rapidly become refractory, with little response to anticonvulsants. Epilepsia partialis continua and other forms of focal seizures are particularly treatment resistant.

In parallel to the epilepsy, a progressive neurologic deficit evolves, with a more severe decline in children compared to adolescents and adults. It is caused by the chronic inflammatory process. Cytotoxic T lymphocytes containing granzyme B, a protein that induces apoptosis in attacked target cells, kill neurons and astrocytes within the affected hemisphere. The immunological target, i.e., the “cause” of the condition, remains unknown. Recent work elucidated the role of the microglial cells and nodules: Even in early disease stages without obvious inflammation, there is microglial activation with upregulation of the inflammasome and of endosomal Toll-like receptors. This attracts T cells, which invade the growing microglial nodules and finally attack the neurons.

The encephalitic nature of this disease has stimulated many attempts to treat it by immunological means, i.e. by approaches meant to counteract elements or activities of the immune system. Unfortunately, immunotherapies may slow down the destructive process but do not positively influence the severe seizure disorder. The only effective therapy for the often very troublesome epilepsy remains the resection or disconnection (hemispherectomy, hemidecortication, functional hemispherectomy, or hemispherectomy) of the affected hemisphere. Such an operation (but not any type of focal resection) offers a very good chance of enduring seizure freedom (>80%).

PROGRESS AGAINST PROGRESSIVE MYOCLONUS-EPILEPSY

Berge A. Minassian, MD and colleagues

The brain is the largest gene employer of all organs. As such, there are tens of thousands of individual ways its development and function can go awry. The vast majority of these ways happen prenatally, often preventing live birth, or during postnatal development. As such most single gene defect disorders present in childhood, and most of Pediatric Neurology really is single gene defect disease. With the progress in genomics, we are now able to specify the disease cause for most of our patients. Knowing this cause allows us to target it. The latter is done through multiple possible ways including protein replacement therapy (e.g. CLN2, to be highlighted in the lecture), viral-mediated gene replacement, viral-mediated gene editing, antisense-oligonucleotide (ASO) gene function downregulation (e.g. in Lafora disease, detailed below and to be highlighted in the lecture), ASO mediated mRNA stabilization, and small molecule targeting of affected gene product. This lecture will review where we are with each of these approaches in neurology and the strengths and limitations of each approach. The audience should be able to perceive the shape of the future of neurology, at least as it is being sketched today.

Almost 130 years after the first PME was described by Unverricht, we now know if not all certainly most diseases in this class. By definition, they afflict and over time devastate previously healthy individuals, by far more commonly children. Nearly all are recessive single-gene defect disorders. This combination of health prior to onset, and causation limited to a single gene make the PME prime candidates for gene-based therapies. Most are lysosomal diseases, conferring an additional advantage (e.g. CLN2, to be detailed in lecture). This lecture will cover the history of the PME and the salient features of each of the member diseases, highlighting how the worst of the epilepsies are first in line for life-saving gene-based treatments. There are living healthy children with PME today who will grow old.

Lafora Disease (LD) is an autosomal recessive, progressive myoclonic epilepsy caused by mutations in the EPM2A (laforin) or EPM2B (malin) genes. The onset is typically in adolescence followed by rapid decline and death within 10 years. LD is characterized by increased glycogen levels with the accumulation of Lafora bodies (LB) which are poorly branched and insoluble glycogen in different tissues. Glycogen Synthase 1 (Gys1) knockout in LD mouse results in an absence of LB formation, glycogen levels are significantly decreased, and neurodegeneration is prevented. We are evaluating the therapeutic potential of Gys1 inhibition using antisense oligonucleotides (ASO) to suppress Gys1 activity in LD mouse models. ASOs targeting mouse Gys1 were identified, characterized, and used to treat LD mice. LD mice treated with the Gys1 ASOs showed a dramatic reduction in brain Gys1 mRNA (75%-90%) and protein (90%) leading to a dramatic reduction in glycogen levels in the brain and a robust reduction of LB formation. Our results demonstrate that glycogen accumulation and LB formation can be halted with anti-Gys1 therapy provide positive proof-of-concept that supports development of ASO therapy for Lafora disease that has the potential to substantially modify the course of this catastrophic and fatal adolescent-onset epilepsy.

DETERMINATION OF CRITERIA FOR CLASSIFICATION OF PEDIATRIC EPILEPSY SURGERY CENTERS.

WD Gaillard

There are no universally established criteria for pediatric epilepsy centers. Several countries provide levels of care for epilepsy surgery in general, but they vary in detail and in process. The current survey is an effort by the ILAE pediatric epilepsy surgery task force to build consensus on criteria for different levels of care founded on complexities based on etiology, location and extent of resection linked to skills, resources, and technology necessary to support these complexities

We employed a modified Delphi method. After preliminary data generated from ILAE task force members that suggested we establish 2 levels of care. We launched a two stage process one based on complexities of care to define the two levels and then personnel and materials necessary to support the two levels. We identified participating sites based on prior ILAE survey participation, task force members, and ILAE regions with recognized epilepsy surgery centers. 80 centers across the world were invited; 60 participated. Consensus was reached when 75% of responses agreed. Two to three rounds of clarifying questions were circulated to clarify question ambiguities and to build consensus.

The 60 centers represented 6 continents, and 20 countries. WHO economies: high income 77%, upper middle income 17%, lower middle income 7% ; The range of first pediatric epilepsy resections range mean 35; median 28; range (2-165); 35 centers operate on >10 young adults year.

Level I: Children age 9 years and older, discrete lesions such tumors, cavernoma, hippocampal sclerosis (plain), cysticercosis; involves lesionectomy, temporal lobectomy, and/or convexity away from eloquent cortex, and includes VNS. Resources deemed standard to support Lev el I care included: child neurologist; pediatric epileptoligist, social worker, general neurosurgeon, anesthesiologist skilled with children, rEEG. Prolonged vEEG, CT, and 1.5 T MRI.

Level II: Includes all higher levels of complexities. Children 8 years and younger; stroke/ischemia, sturge weber, AVM, encephalomalacia. Post inflammatory, Rasmussen's, Tuberous Sclerosis Complex, hippocampal sclerosis dual pathology, hypothalamic hamartoma, MRI negative, poorly demarcated lesions (unclear margins/borders); extra-temporal lobar, multi lobar, hemispheric, multifocal, Interhemispheric, subcortical. Involving eloquent cortex, insula, or basal brain regions; DBS, RNS; and, children with encephalopathy, regression, associated developmental or medical syndrome, genetic abnormalities. Complicated medical problems, ongoing status epilepticus; Resources deemed standard to support Level I care included: 1) Personnel: child neurologist; pediatric epileptoligist, pediatric s neurophysiologist; pediatric (epilepsy) neurosurgeon., functional/stereotactic epilepsy neurosurgeon, pediatric neuropsychologist, child psychiatrist, pediatric neuro-radiologist, social worker, pediatric neurology nursing, epilepsy pathologist , pediatric anesthesiologist, nutritionist/dietician, coordinator. Certified EMU (pediatric); 2) Technology: rEEG, long term vEEG, intraoperative ECOG, CT. 3T MRI. EPI fMRI DTI tractography, angiography, some kind of functional imaging (PET) some form of source localization capability, functional mapping (fMRI, cortical mapping), and invasive recording (intraoperative ECOG, subdurals, sEEG), neuro-navigation; 3) Resources: Dedicated pediatric services, a PICU and rehabilitation facilities. Intraoperative MRI, TMS, minimally invasive mapping are not yet deemed required,

There was no consensus regarding corpus callosotomy, psychiatric comorbidity, and intellectual disability/disorder. There was consensus NOT to further split Level II. However there was (near unanimous) view for the following age less than 24 months; Multifocal, Around eloquent cortex, Normal MRI, indiscrete poorly demarcated lesion; Tuberous Sclerosis Complex, Hypothalamic Hamartoma, Insula, Multi-lobar resections.

Conclusion. In international modified Delphi process identified criteria for defining two levels of care for establishing or characterizing pediatric epilepsy surgery centers based on clinical features and surgical approaches. Criteria were also identified for skills, personnel, and technology necessary to support those levels of care. In addition there was (near unanimous) agreement for concerning the youngest patients with that most demanding surgical procedures. There findings should support initiatives to standardize and elevate care of children with pharmaco-resistant epilepsy. While we defined the need for neurologists, epileptologists, neurophysiologists, and pediatric epilepsy neurosurgeons we did not address what training defines that expertise.

NEUROSTIMULATION IN EPILEPSY: SOME PROVOCATIVE THOUGHTS

Philippe Kahane, Grenoble, France

There are many ways to stimulate non-invasively or invasively the human epileptic brain, either by manipulating remote control systems, or by interfering directly with the epileptogenic zone. These are palliative methods, which mainly aimed at reducing the frequency and severity of seizures in refractory epilepsy patients for whom surgical resection is not feasible. Some are CE and/or FDA approved (vagus nerve stimulation, transcutaneous stimulation of the trigeminal nerve, stimulation of the anterior nucleus of the thalamus, adaptive cortical stimulation), but most remain experimental. We will review here the advantages and limits of these methods, of which most need to be further evaluated.

WHICH ANIMAL MODELS ARE RELEVANT TO EPILEPSY SURGERY CANDIDATES?

Aristea S. Galanopoulou MD PhD

Animal models of seizures have been extensively utilized to better understand the mechanisms underlying seizure generation and epileptogenesis as well as to identify better treatments to prevent or ameliorate epilepsy and its comorbidities. Several of these models are etiologically relevant to human epilepsies while others share important phenotypic features or pathologies characteristic of human epilepsies. Of particular clinical interest are the animal models that relate to epilepsy surgery candidates. These include models of drug-resistant seizures, such as models of post-status epilepticus drug-resistant epilepsies, kindling induced seizures, or post-traumatic epilepsy. *In vitro* models of drug-resistant seizures can be produced either via use of organotypic cultures or acute slices, including brain slices from individuals who underwent epilepsy resection surgery. Other models may model etiologies common among epilepsies requiring surgical evaluation, such as genetic models predisposing to drug-resistant epilepsies, tumor-associated epilepsies, models of cortical malformation or dysplasias. Animal models have also been used to optimize or provide proof of concept for new surgical treatments, such as viral vector delivered treatments, closed loop control of seizures, transplantation of specific cell types. This presentation will summarize selected of these models that are relevant to epilepsy surgery candidates with particular emphasis upon their contribution on identifying mechanisms and more potent therapies for epilepsy.

BRAIN SOMATIC MUTATIONS IN GENES OF THE MTOR PATHWAY CAUSE EPILEPSY ASSOCIATED TO MALFORMATIONS OF CORTICAL DEVELOPMENT

Sara Baldassari, Théo Ribierre, Sarah Ferrand-Sorbets, Georg Dorfmüller, Mathilde Chipaux and Stéphanie Baulac

Malformations of cortical development, including focal cortical dysplasia (FCD) and hemimegalencephaly (HME), are major causes of pediatric refractory epilepsies subjected to surgery. Enlarged dysmorphic neurons (DNs) and balloon cells (BCs) are pathological hallmarks of FCD (type 2) but their origin remains unknown. Strong evidence supports a genetic origin. Here we aimed to provide guidelines for molecular testing.

We collected in a monocentric study 80 operated children with drug-resistant epilepsy and a neuropathological diagnosis of FCD1, FCD2 or HME. Targeted sequencing (≥2000X) of matched brain-blood samples was used to detect low-rate mosaic variants in mTOR-pathway and FCD genes.

We achieved a high diagnostic yield, elucidating 29% of FCD1 cases and 63% of FCD2/HME cases. FCD1 cases carried pathogenic somatic variants in N-glycosylation pathway-associated SLC35A2. FCD2 cases carried somatic gain-of-function variants in MTOR and its activators (AKT3, PIK3CA, RHEB), as well as somatic and germline loss-of-function variants in its repressors (DEPDC5, TSC1, TSC2). Variant allele frequencies were higher in HME than FCD reflecting the timing of mutational event. Sequencing of microdissected cells demonstrated that >90% of DNs and BCs are mutated, supporting the conclusion that their presence correlates with a positive genetic diagnosis. No correlation between a given mutated gene and surgical outcome emerged.

This study unveils two distinct pathogenic mechanisms involving the non-mTOR-related gene SLC35A2 in FCD1, and mTOR-pathway in FCD2/HME, orienting towards targeted therapies. We provide a framework for efficient genetic testing in FCD/HME, stressing that the molecular diagnostic yield reflects the neuropathological findings.

PHENOMENOLOGY DEPENDENT APPROACH OF EPILEPSY TREATMENT / HYPOMOTOR SEIZURES

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Hypomotor seizures appear in infants, small children and nonverbal patients. The essential main feature of hypomotor seizures is arrest of behavior but this feature may indicate several different symptoms: a subjective feeling, impaired awareness or hypokinesia. Even subtle clusters of spasms may occasionally appear as hypomotor seizures. Because of the young age of the patients, the poor co-operation and verbal abilities and difficulty to test awareness, it is not possible to determinate the exact nature of the hypomotor symptom and to classify the seizures further.

While the main feature is the arrest of behavior, subtle additional symptoms such as autonomic symptoms, apnea, unsustained head or eye movements and small mouth automatism are often seen during hypomotor seizures.

Most of the hypomotor seizures prove to be focal seizures but infrequently also generalized seizures (absences) may appear as hypomotor seizures. The origin of focal hypomotor seizures is most often in the temporal lobe but hypomotor seizures were described to originate also from parietal, occipital or frontal lobe. (Hamer et al 1999, Källen et al 2002, Yu et al 2013)

The special features of seizure semiology in small children are only partly due to the difficulties in testing awareness or finding out about the subjective symptoms. Also the normal maturation of the brain by age has impact on the semiology of the epileptic seizures. The maturation of the nervous system enables more complex gross and fine motor movements and concurrently also more elaborate motor manifestations of the seizures.

In this presentation, we go through the case of a young boy who started to have hypomotor seizures at the age of one year and follow the evolution of his seizures until school age.

EVIDENCE BASED SUCCESS OF EPILEPSY SURGERY IN CHILDREN

Bertil Rydenhag, professor of Neurosurgery, Sahlgrenska University Hospital, Gothenburg, Sweden.

There are three randomised controlled studies (RCT) (1-3) in epilepsy surgery, all of them giving favorable data to promote epilepsy surgery instead of continued medical treatment only. The most recent one deals with children (1). The basic design in two of the studies (1, 3) was to use the fact that the typical waiting time for surgery was 1 year. The patients that were randomized to surgery were operated within one month; the others were on continued medication for one year. However, the ERSET-study (which included children from 12 years of age) was a multi-centre study with randomisation to medical treatment for two years or early surgery (2). It is very important how to define "success" in epilepsy surgery. Regarding the seizure outcome there are different scales used, and it is important to identify the subpopulation of patients that get sustained seizure freedom since surgery (4-6). In addition, children may need special considerations where these scales may not suffice (7). Not only the seizure outcome, but also the risk of a complication at the presurgical evaluation, invasive or not, and the surgery must be considered (8-10), as well as cognitive outcomes (11) and neuropsychiatry (12). Children are supposed to ahead of them. Long-term outcomes are thus even more important than in adults (13). Since it is not possible to answer every question with an RCT it is important to take well done observational studies into consideration for the evaluation of epilepsy surgery in children (14). These different outcome measures and evidence of epilepsy surgery success will be presented and discussed at the lecture, including the potential risks.

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THE EUROPEAN REFERENCE NETWORK FOR RARE AND COMPLEX EPILEPSIES EPICARE

J. Helen Cross

Coordinator ERN EpiCARE, 2017-2019

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It has become increasingly apparent that epilepsy is not a single condition, but a symptom of a group of rare diseases. Traditionally treatments have been targeted at the seizures with little understanding of the underlying cause; advances in structural brain imaging as well as molecular and metabolic diagnostics have determined there to be an increasing number of causes resulting in the description of in excess of 130 rare diseases. With an understanding of underlying cause, treatments can be more targeted. The relative prevalence of each disease means a coordinated approach is required across key centres of expertise, with the development of e-tools to enable complex diagnostic and therapeutic interventions in a wider number of patients across Europe. Only then can we increase the possibility for new treatments that can be integrated into the clinical care pathway

In 2013 E-pilepsy, was one of two pilot European reference networks given funding to be developed over a period of three years. The aim of this network was to raise awareness and availability of epilepsy surgery across Europe. This was initially a network of 13 partner and a further 11 affiliated centres that ultimately achieved participation of 52 centres across Europe; a website was developed with information translated into 13 languages. Monthly case discussions were established, with development of web based tools such as post processing MRI, and neuropsychology assessment initiated. In 2016 DG Sante called for proposals for the development of European Reference Networks for rare diseases. 24 networks were agreed by the board of member states including EpiCARE, an ERN for rare and complex epilepsies.

The EpiCARE network (www.epi-care.eu), for the clinical care and management of individuals across Europe with rare and complex epilepsies, was developed as an extension from the pilot reference network, E-pilepsy. EpiCARE is a network of 28 centres with expertise in the rare and complex epilepsies, developed to enhance diagnosis and ultimate management of this group of disorders, located across 13 countries. It is recognized that delivery of expertise can be enhanced through the use of e-tools, minimizing the need for patients to travel ensuring the delivery of optimal health care at a local level. E-pilepsy continues as the surgical therapeutic arm of EpiCARE, and has continued with case discussion at the European level. However, there are now both 5 diagnostic (laboratory diagnostics, neurophysiology, neuroimaging, neuropsychology and neuropathology) and a further 3 therapeutic work packages (neonatal seizures, targeted medical therapies and dietary therapies), all established and working toward harmonization and availability of diagnosis and care of the rare and complex epilepsies. There are also cross cutting themes including registry and guideline development, education and training, research and clinical trials. With the aim of enhancing clinical care in the first two years of its existence we have initiated regular review and discussion of non-surgical cases with a clear care pathway as well as maintaining the surgical discussions on a monthly basis. A knowledge of current standards of care has been established across all areas, and further progress made with regard to the development of a registry to suit both clinical and research purposes. Patient support groups through ePAG (Patient Advisory Group) have been present at all levels of discussion, and will be key as we move forward in further development of the network.

CANNABINOIDS IN THE MANAGEMENT OF THE EPILEPSIES

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There has been much recent heightened interest in the possible use of cannabinoid products in the treatment of complex epilepsies, with anecdotal reports of dramatic benefit in otherwise drug resistant individuals. Although systematic studies have now been undertaken and reported showing benefit of cannabidiol (CBD) as Epidiolex (GW Pharma) in the treatment of seizures associated with Dravet and Lennox Gastaut syndromes, there remains much confusion with the role of hemp oils and other products (CBD with tetrahydrocannabinol) for which there is no quality assured consistent product or evidence base for use. There is also much debate as to whether the psychoactive component, tetrahydrocannabinol is required for optimal effect, with no sound evidence base for support, and concern as to safety with regard to further effects on the developing brain. The current position is that that data has been acquired for Epidiolex, and license for use granted by the US Federal Drug Administration, with data submitted to the European Medicines Authority for review. Other products with THC content have been reported to be beneficial although only in open label studies, with results that could be considered little different to the randomized controlled trials with cannabidiol alone. Although benefit in certain specific complex epilepsies has been demonstrated with CBD, the requirement or not for some THC for added benefit remains under debate and as yet unproven.