EPILEPSY

FP37

BONE HEALTH SCREENING PRACTICES AMONGST BOSTON CHILDREN'S HOSPITAL NEUROLOGISTS IN PEDIATRIC EPILEPSY PATIENTS: FOLLOW UP ON A QUALITY IMPROVEMENT PROJECT

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Aim: Pediatric epilepsy patients are at risk for osteopenia and fractures. Risk factors include being non-ambulatory, decreased sun exposure and reduced vitamin D levels from antiepileptic medications. Prior studies suggest that neurologists do not routinely screen for bone health when treating epilepsy patients. We surveyed paediatric neurologists at our centre on bone health care in paediatric epilepsy patients.

Methods: Baseline practices of paediatric neurologists with respect to bone health in epilepsy patients was assessed by surveying all neurologists in our centre. An intervention including education and developing a standardized screening and treatment protocol was implemented. Chart review to evaluate effectiveness was performed one and six months post intervention.

Results: Our survey showed that 67% of providers estimated that they screen for bone health <25% of the time. An algorithm was developed to standardize screening and treatment in our centre and all members of the division were educated. After six months of the intervention, Vitamin D levels were checked in 19.5% of epilepsy patients during routine clinic appointments, compared to 2.4% before the intervention, and 12.4% one month after intervention. Six months post intervention, 23% of patients were on vitamin D supplementation of at least 400 International Units.

Conclusions: At baseline, the majority of paediatric neurologists at BCH did not routinely screen for bone health in paediatric epilepsy patients. Findings prompted us to develop a standardized screening and treatment algorithm in order to improve awareness and patient care. Follow up chart reviews suggest improved screening and prescription practices after our intervention.

FP38

CLINICAL, EEG AND IMAGING CHARACTERISTICS OF CHILDREN WITH STURGE-WEBER SYNDROME: A PROSPECTIVE, LONGITUDINAL STUDY

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Introduction: Reliable markers of neuro-cognitive progression during the clinical course of Sturge-Weber syndrome (SWS) have not been established. In this prospective, longitudinal clinical research study of children with SWS, we have correlated the electro-clinical features, imaging characteristics and cognitive functions (IQ) in a single-center cohort.

Methods: Gender, age, scalp EEG abnormalities (background attenuation, slowing, spike frequency), and extent of brain involvement on MRI were correlated with epilepsy variables and IQ in SWS children at baseline (n=65, 63 unilateral, 2 bilateral; mean age: 3.9 years, 3 months – 12.7 years) and at follow-up (n=38, mean follow-up: 2.3 years). Results: Girls (n=41) were younger (2.7 vs. 5.8 years, p<0.001), had earlier seizure onset (mean: 0.9 vs. 2.1 years; p=0.015) and shorter epilepsy duration (1.9 vs. 3.5 years; p=0.015) than boys; extent of brain involvement, seizure frequency and IQ showed no gender differences. Initial mean IQ was 80±20, and lower initial IQ was associated with EEG background abnormalities and extensive brain involvement (p<0.01). Lower IQ at follow-up was associated with initial EEG background abnormalities (p=0.001) and high spike frequency (p=0.003) but not extent of brain involvement. Interictal spikes were present in 20 patients but were lateralized to the unaffected hemisphere in 6 (30%).

Conclusions: EEG background abnormalities and high spike frequency are better predictors of poor cognitive outcome in young SWS children than the extent of brain involvement on MRI; however, interictal spikes may often be falsely lateralizing. The observed gender differences in epilepsy characteristics warrant further studies in larger SWS cohorts.

FP39

HIGH PREVALENCE OF AUTOANTIBODIES TO N-METHYL-D-ASPARTATE RECEPTOR AND THE EFFICACY OF GLUCOCORTICOIDS IN PCDH19-RELATED FEMALE-LIMITED EPILEPSY

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Introduction: A genetic abnormality in ***PCDH19*** causes infantile-onset intractable epilepsy in females (i.e., ***PCDH19***-related female-limited epilepsy, ***PCDH19***-FLE). This condition is characterized by recurrent seizure clusters often involving limbic structures and frequently precipitated by febrile illness. Autoantibodies to ***N***-methyl-D-aspartate receptor (NMDAR-Abs) cause limbic encephalitis, but also appear in some patients with epilepsy, suggesting a possible link between NMDAR-Ab-mediated inflammatory processes and the pathogenesis of the epilepsy.

Methods: To examine whether such immune processes are involved in ***PCDH19***-FLE, NMDAR-Abs in the serum and/or cerebrospinal fluid (CSF) were analysed in 8 Japanese patients by using an enzyme-linked immunosorbent assay or immunoblotting assay. Glucocorticoid treatment efficacy was also evaluated in 4 patients.

Results: Titers of NMDAR-Abs taken within 6 years of disease onset were significantly elevated in the serum of 7/8 patients (87.5%) and in the CSF of 4/6 patients (66.7%). However, in a follow-up evaluation of 3 patients, serum titers were reduced. Although seizures were refractory to anticonvulsants, glucocorticoids immediately suppressed ongoing seizure clusters in all 4 patients who received them; specifically, 10–30 mg/kg of intravenous methylprednisolone for 3 days was effective in 3 patients aged 3 years or younger, and 1 mg/kg oral prednisolone was effective in 1 patient aged 11 years.

Discussion: The prevalence of NMDAR-Abs was extremely high in patients with ***PCDH19***-FLE, particularly during the early disease stages. Although the clinical significance of NMDAR-Abs remains unclear, the immediate anticonvulsant efficacy of glucocorticoid treatment suggests that increased vulnerability of the blood–brain barrier to systemic inflammation might underlie ***PCDH19***-FLE pathogenesis.

FP40

AUTISTIC CHILDREN WITH EEG ABNORMALITIES AND/OR EPILEPSY: CLINICAL CHARACTERIZATION IN TWO INDEPENDENT SAMPLES

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Introduction: several studies have reported a high frequency of epilepsy and/or co-occurrence of EEG abnormalities in children with autism spectrum disorder, although the incidence rates vary between 5% to 46%.

Methods: we analysed two different samples of non-syndromic ASD patients: an original sample encompassing 432 Italian patients and a replica sample including 714 Caucasian American patients recruited by the Autism Genetic Resource Exchange Consortium. Comparable clinical, biological and developmental variables were correlated in both samples with "presence/absence of epilepsy" or "presence/absence of EEG abnormalities", and tested for association between each variable and biological endophenotypes by non-parametric Kendall τ and Kruskal-Wallis ANOVA.

Results: in the experimental sample and in the replica sample, ASD patients positive for EEG abnormalities display a significant association with a lower risk of familial history for autoimmune/allergic diseases (Italian and AGRE sample: τ= -0.115 and -0.252, respectively; both P<0.05), and those affected by epilepsy are characterized specifically by verbal language delay in the absence of a generalized neurodevelopmental delay (Italian and AGRE sample: τ= 0.100 and 0.073; both p<0.05). Interestingly, Italian patients with EEG abnormalities show significantly lower serotonin blood levels (τ=-0.183; P<0.01).

Conclusions: these results extend previous findings, by supporting a deleterious effect of EEG abnormalities on verbal language

development, and by pointing toward a protective role against the development of epilepsy for a family history of autoimmune/allergic diseases and elevated serotonin blood levels.

FP41

CLINICAL MARKERS OF POSTICTAL GENERALIZED EEG SUPPRESSION (PGES) IN CHILDREN

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Aim: Postictal generalized EEG suppression (PGES) has been proposed as a neurophysiological marker for sudden unexpected death in epilepsy (SUDEP). If PGES is a marker of potentially fatal seizures, it is critical to identify clinical features that distinguish people with epilepsy that are prone to PGES.

Methods: A retrospective review of vEEG at the Hospital for Sick Children (2009-2011) was performed, to identify episodes of PGES as defined by Surges et al, 2011, along with clinical features of paediatric patients at the time of PGES recording.

Results: 26 children (62%; 16 male) demonstrated 49 seizures with PGES (37%) from a total of 134 seizures. Duration of PGES ranged 2-54 sec (mean 30 sec). 42 of 48 (88%) seizures associated with PGES were generalized tonic clonic seizures (GTCS). Duration of 42 PGES with GTCS (mean 35 sec) was significantly longer than that of 6 PGES without GTCS (mean 9.6 sec; $p < 0.005$). Longer PGES duration significantly correlated with lower E-Chess score, a marker of epilepsy severity ($R = 0.63$; $p < 0.001$) and with less lifetime use of AEDs ($R = 0.40$; $p < 0.05$). 8 children had global developmental delay (31%) and had a shorter PGES duration (mean 17.7 sec) compared to those children with normal development (mean 37.7 sec; $p<0.005$).

Conclusion: Longer duration of PGES in children significantly correlates with GTCS, lower E-Chess score, less lifetime use of AEDs and normal development. The latter three findings suggest that PGES is more common in pediatric patients with less severe epilepsy.

FP42

WHO ARE THE SUPER RESPONDERS TO THE KETOGENIC DIET?

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Introduction: The ketogenic diet (KD) is mainly used in pharmaco-resistant epilepsy. However, some seem to respond dramatically to the KD while others take several months to years to have complete cessation of the seizures.

Methods: A retrospective study was done of all those who responded with complete cessation of seizures in less than four weeks (super responders) in all our patients since 1996.. We looked at the impact of age, seizure type, seizure syndrome, duration of seizures prior to institution of the KD and keto ratio.

Results: Of a total of 205 patients (ages from 4 months to 57 years), 11 patients were super-responders. Of these 8 patients had symptomatic epileptic encephalopathy, 2 had localization related epilepsy with no lesion and 1 had localization related epilepsy with lesion. Except for two, the rest (9) had their first seizure before the age of one year. KD was begun between 7 -61 months after the onset of seizures (mean 25.2 months) while in delayed responders the average was 74.9 months. The keto ratio was less than 2:1 in four, in four it was between 2:1 and 3:1 and in three it was between 3:1 and 4:1.

Conclusion: Super responders are usually younger in age and those put on KD earlier. Epileptic encephalopathy seems to respond better. Individual keto ratio is not significant. Most other authors too have found the same results.

FP43

SUCCESSFUL USE OF FENFLURAMINE AS ADD-ON TREATMENT IN DRAVET SYNDROME: A THREE YEARS PROSPECTIVE FOLLOW-UP

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Purpose: Evaluation of efficacy of fenfluramine as an add-on anti-epileptic drug in Dravet syndrome.

Methods: Dravet syndrome remains, notwithstanding the introduction of newer anti-epileptic drugs, a therapy resistant and catastrophic epilepsy syndrome.

Fenfluramine is an amphetamine-like drug often used in the past as part of anti-obesity treatment. Because of possible cardiac side effects (valve thickening, pulmonary hypertension), it has been withdrawn from the market in the US and Europe. In Belgium, it was allowed to study its potential anti-convulsive effect in a small group of well-defined patients with Dravet syndrome.

Results: Twelve patients, seven girls and five boys, with a genetically proven (11/12) diagnosis of Dravet syndrome received add-on therapy with fenfluramine.

The retrospective data were published in 2012 (Ceulemans et al, Epilepsia 2012 Jul; 53(7):1131-9). We now present the results of 3 years prospective follow-up of ten patients of this group, including two new patients Children were carefully monitored for reduction of seizure frequency and cardiac side effects. Mean age ranged from 3 - 35 years. Dosage of fenfluramine was 0, 34 (0, 12-0, 90) mg/kg/d. All patients had at least a >75% of reduction of seizures in the study period of 3 years. Eight out of twelve were seizure free for at least one year. Three were seizure free for the complete trial period.

In four patients a mild thickening of 1 or 2 cardiac valves, without clinical significance, was seen. The mitral valve seems to be the most frequently damaged valve. Only one patient had valve thickening on each ultrasound cardiac examination. Loss of appetite (4 patients) seems not a major problem.

Conclusions: These new prospective data confirm the promising results from the long-term retrospective study of fenfluramine as add on anti epileptic medication in Dravet syndrome. Eight out of twelve patients (66%) remained seizure free for at least for one year. The mitral valve seems to be the most vulnerable for valve thickening by this drug. Realising that this observational study has limitations, a larger prospective study is under way, now the drug has recently be granted as orphan drug designation in Europe and the US.

FP44

USEFULNESS OF VIDEO-EEG MONITORING IN CHILDREN

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Aim: To analyse the sensitivity of the v-EEG for detecting clinical events and analyse therapeutic changes after the reading.

Method: A retrospective, descriptive study of 178 paediatric v-EEGs recordings at the Hospital Italiano de Buenos Aires from January 2011 to February 2012. The V-EEG were divided in: With epileptic clinical events, with nonepileptic clinical events and Uneventful. We analysed the therapeutic changes. The data were analysed using univariate statistics.

Results: Age was: 1 month to 17 years (median 9.1). Clinical events were recorded in 120/178 (67.4%), 81/178 (45.5%), were Epileptic and 39/178 (21.4%) non-epileptic. The sensitivity of the v-EEG divided by duration was: 6 h 71.2%, 24 h 68.9% and 48 h or more 78%. According to the age distribution, the sensitivity was 69.8% in pre-schoolers, 58.97% in school and 82.14% in adolescents. The sensitivity for detection of clinical events was better in 6 hrs. v-EEG in pre-schoolers ($p < 0.05$) and in 48 hrs. v-EEG in all ages ($p < 0.05$). The therapeutic approach was changed in 72/178 (40.4%). AEDs were indicated in 9.75%, AEDs were modified in 63.9%, AEDs were suspended in 2.75%, epilepsy surgery was indicated in 9.75%, were referred to mental service health 9.75% and ketogenic diet was indicated or suspended in 4.1%.

Conclusion: The v-EEG was useful for the detection of clinical events in two thirds of the patients and the sensitivity was higher in those that lasted two days or more. The modification of AEDs was the most frequent therapeutic change.

FP45

TRAJECTORIES OF HEALTH AND WELL-BEING IN CHILDREN WITH EPILEPSY: HYPOTHESES AND METHODOLOGY OF A CANADIAN LONGITUDINAL STUDY

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Aim: Our study quantifies direct, mediating and moderating influences of various epilepsy, co-morbid, child, and family variables on children's health and well-being over the early life-course. We will present hypotheses and methodology of this prospective longitudinal study based on a conceptual framework for understanding health outcomes.

Methods: The population is children with epilepsy 8-14 years old and their caregivers from across Canada. Children, caregivers, and health professionals complete 17 measures at five visits over 28 months. The measures are all based on content, the source of the items, psychometric properties, and provision for child self-report. Our cross-sectional and longitudinal design includes a relational model for structural equation modelling of specific biomedical and psychosocial variables with hierarchical direction of influence. We use hierarchical linear modelling to measure change over time.

Results: Demographics: among 506 families: mean child age 11.4-years; epilepsy onset 6.2 years; epilepsy duration 5.2 years; and mean IQ 99.4. Characteristics: 71% take a single medication; 46% have experienced medication failure; 29% have been seizure free, 31% had low and 37% high seizure severity over the previous year.

Conclusion: Discussion of these perspectives will help researchers consider their methodology and encourage longitudinal studies. Furthermore, our experience may help clinicians identify what to look for when evaluating outcomes research. We believe that the next generation of research to understand life-course effects on the lives of children and youth with chronic conditions and their families must occur over real time.

FP46

CLINICAL FEATURES AND GENE MUTATIONAL SPECTRUM OF CDKL5-RELATED DISEASES IN A COHORT OF CHINESE PATIENTS

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Aim: In order to clarify the CDKL5 gene mutational spectrum and the clinical features in Chinese patients, CDKL5 mutation screening in cases with early-onset epileptic encephalopathies and Rett syndrome were performed.

Method: The detailed clinical information of 102 Chinese patients with early-onset epileptic encephalopathies and atypical Rett syndrome was collected. CDKL5 gene mutations were analyzed by PCR, direct sequence and MLPA. The patterns of X-chromosome inactivation were studied.

Results: The de novo CDKL5 gene mutations were found in ten patients. The common features of the patients with CDKL5 gene mutations included refractory seizures starting before 4 months of age, severe psychomotor retardation, Rett-like features such as hand stereotypies, deceleration of head growth after birth, and poor prognosis. The X-chromosome inactivation patterns of all the female patients were random.

Conclusion: Mutations in CDKL5 gene account for 12.6% of 71 girls and 3.2% of 31 boys with early-onset epileptic encephalopathies or the Hanefeld variant of Rett syndrome. CDKL5 gene mutations analysis should be considered in both genders, and the test plays an important role in genetic counselling and the judgment of the prognosis of the patients.

FP47

CLINICO ETIOLOGICAL PROFILE OF INFANTILE ONSET EPILEPSY AT A TERTIARY CARE CENTER IN INDIA

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Aim: Infantile-onset epilepsy (excluding infantile spasms) is a poorly understood entity in terms of etiology, prognosis and optimal evaluation. We sought to study clinic-etiological profile, predictors of etiology and seizure control in this group.

Method: Prospective observational study at tertiary care paediatric centre over one year (May 2012-June 2013)

Results: A total 88 children with onset of epilepsy between 2-24 months were enrolled. Mean age of onset 7.27 months (± 4.97); male: female ratio 1.4:1. A definitive cause could be identified in 45 children (51%): 40 were structural, 5 were genetic causes. Commonest structural causes were: static encephalopathies (16/40), and malformations (10/40), and neurocutaneous syndromes (4/40). Neuroimaging was an important predictor of cause: 36/42 patients with abnormal neuroimaging had confirmed etiological diagnosis. Metabolic work-up identified cause in 4 of 10 children (40%) with normal neuroimaging. Good seizure control seen in 31 children at last follow-up (6-12 months). Good response to first drug and requirement of 2 or less drugs predicted good seizure control. Fourteen of 88 (16%) later developed infantile spasms. Prior developmental delay, requirement of 3 or more drugs for seizure control and normal neuroimaging were significant predictors of conversion to infantile spasms.

Conclusion: Infantile epilepsy was of unknown etiology in 49% cases. MRI brain should be first investigation. Static encephalopathies and malformations are commonest causes. Children with normal neuroimaging should undergo metabolic work up. Large, multi-centre prospective studies with tailored genetic testing are needed to better understand etiology, appropriate drugs and long-term prognosis.

FP48

THE ASSOCIATION OF FEBRILE SEIZURE AND SINGLE NUCLEOTIDE POLYMORPHISM OF CYCLOOXYGENASE-2

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Introduction: Febrile seizure (FS) is the most common form of childhood convulsions with an estimated prevalence of 2-5% among children less than 5 years of age. Several polymorphisms have been suggested to be associated with FS including SCN1A, IL-1, IL-1Ra, IL-10… etc. Due to the febrile nature of the disease, possible association of FS and selected single nucleotide polymorphism (SNP) in the cyclooxygenase-2 (COX-2) gene was thus investigated in this study.

Method: A series of FS patients were collected consecutively at one medical centre. IL-1Ra and IL-10 polymorphisms, as well as 9 SNPs in the COX-2 gene were analysed by direct DNA sequencing and restriction endonuclease digestion. The frequencies of SNPs were compared to that of apparent health individuals.

Results: The IL-Ra intron 2 variable tandem repeat polymorphisms did not exhibit significant polymorphic characteristics among analysed FS (n=15) and health individuals (n=10). Both groups carry the predominant allele I. The frequency of IL-10 SNP (rs18000872) also did not exhibit significant difference between two groups. However, a significant difference in frequency was observed in one (rs689466) out of nine analysed COX-2 SNPs. This -1192 A allele exhibits significant higher frequency in FS (70%) than that of health (15%) group ($p<0.05$).

Conclusion: An apparent association between the -1192 A allele in the COX-2 gene and FS is observed. This novel evidence demonstrates the possible role of COX-2 SNP in the pathogenesis of the specific epileptic syndrome FS.

FP49

INFANTILE SPASMS: ICTAL VIDEO-EEG CLASSIFICATION BASED ON THE DELPHI WEST GROUP PROPOSAL

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Introduction: The West Delphi group proposed a classification of infantile spasms (IS): IS in cluster with Hypsarrhythmia (West syndrome), IS in cluster without hypsarrhythmia; IS single-spasms variant (ISSV) with hypsarrhytmia and ISSV without hypsarrhytmia.

Aim: To classify the IS registered in the video EEGs according to the Delphi West group proposal and analyse outcome.

Methods: Observational retrospective study including 33 video-EEGs, between January 2010 and September 2013.

Results: median age: 6.1 months, 19 (57.5%) were female. According to the classification, we observed: 14 (42.4%) had West syndrome (WS), 10 (30.3%) IS in cluster without hypsarrhythmia, 7 (21.2%) ISSV with hypsarrhythmia, and 2 (6%) ISSV without hypsarrhythmia.

24 patients had symptomatic epilepsy and 7 cryptogenic.

EEG findings: 18 (63.6%) presented hypsarrhythmia, 24 (81.8%) multifocal paroxysms and 6 unifocal paroxysms. Fourteen of the 18 (77.7%) patients with hypsarrhythmia, had symptomatic epilepsy.

We analysed 31 patients. 8 (25.8%), were preterm. 23 (74, 2%) had a normal neurological exam before seizures started, 15 (49.5%) worsened developmental delay. One patient died. The median duration of IS was 4 months (IQR 1, 5-9), 4 months in patients with hypsarrhythmia and 6.5 months, without hypsarrhythmia.

Outcome: 13 developed refractory epilepsy, 10/13 had symptomatic epilepsy and 10/13 had hypsarrhythmia.

12 out of 17 (70, 5%) patients with hypsarrhythmia and 3/12 (25%) patients without hypsarrhythmia lost developmental skills. (p: 0.01).

Conclusions: We observed a high frequency of patients with West syndrome and ISSV without hypsarrhythmia. Patients with or without hypsarrhythmia developed refractory epilepsy associated to developmental delay, being more frequent in patients with hypsarrhythmia.