

Society Proceedings

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**1. Studies in the quality of life in childhood epilepsy: Materials, methods, “mea culpa”—Blandine Gallet, Pauline Duhard, Inès Boudrière, Anne Barbaud, Caroline Rouvellat, Cécile Alquier, Homan Cheng, Paul Hwang (Université de Toulouse and Paediatric Neurology, North York General Hospital, University of Toronto Epilepsy Research Program, ON, Canada)**

In a series of sequential studies from 2003 to 2007, we examined the quality of life in children with epilepsy, partial and generalized, on and off AEDs. All children came from a community-based practice referred to a paediatric neurologist (PAH) and were followed using standardized problem-oriented medical records. EEGs were all performed on Harmonie©, from Stelate©, Montreal, QC with electrodes in 10–20 positions, EOG, chin EMG and ECG.

Two methods of assessing QOLIE used the Cramer (2002) and the Ronen (2005) scales, both validated and applied consistently. Behavioral measures used the SNAP IV 26-item questionnaire of Swan (1975). Statistical tests applied included *t*-tests, Chi-square.

In four serial studies over five years, in 80 children, the major finding was a significant improvement in QOLIE among seizure-free children compared to seizure-prone, with better behavioral outcome: in attention, hyperactive and oppositional subscales in SNAP IV test. No significant differences were found among different AEDS, levels of drugs, partial vs. generalized seizures or remission of epilepsy.

Our studies show the reliability and validity of QOLIE measures currently available, their statistical analysis and application to behavioral and prognostic outcome, but leave open the question of sensitivity to age-specific maturational changes or drug effects.

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**2. Development of interictal spikes following status epilepticus from intrahippocampal pilocarpine—Jonathan Kleen, Pierre-Pascal Lenck-Santini, Gregory Holmes (Dartmouth Medical School, Hanover, NH, USA)**

EEGs during interictal periods often show bursts of high-amplitude spikes that stem from groups of aberrant neurons discharging synchronously. Depending on the brain region where they originate, interictal spikes may briefly disrupt neural processes occurring in that particular region, and are thus hypothesized to contribute to cognitive slowing over time. We are investigating interictal spikes with a modified rat model of temporal lobe epilepsy. Pilocarpine (1 mg) infusion into the ventral CA1 region of the hippocampus produces well-delineated interictal spikes. With depth electrodes in both hippocampi as well as the ipsilateral right prefrontal cortex, and we observed the time course of the development of spike-generating foci at the infusion site ( $n = 5$ ), with spikes emergent at 11–14 days post-infusion. All rats developed interictal spikes, though two rats required a second infusion. Spontaneous seizures are generated at the infusion site, but have been somewhat infrequent in this model. We have also observed the establishment of independent spike-generating mirror foci in the contralateral hippocampus and similar spike foci in the prefrontal cortex. The autonomous spike foci may have synergistic impact on working memory processes concerting between these regions. To examine functional neural circuitry disruption by spikes, we are utilizing an operant behavior task called delayed-match-to-sample (DMTS), which employs hippocampal-dependent short-term memory. We are assessing whether animals make more errors on trials with spikes than trials without, which avoids confounding variables and allows the analysis of consequences of spikes in specific epochs of the task, to isolate memory encoding vs. recall, etc. We are also weighing the influence of the autonomous spikes engendered in the each hippocampi versus the ipsilateral PFC.

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### 3. Asymmetric features of EEG and response to treatment in juvenile myoclonic epilepsy—Karine Letourneau<sup>1</sup>, Charles Deacon<sup>1</sup>, Cecile Cieuta Walti<sup>2</sup> (<sup>1</sup>Departments of Neurology, Centre Hospitalier Universitaire de Sherbrooke, Quebec, Canada, <sup>2</sup>Neuropediatrics, Centre Hospitalier Universitaire de Sherbrooke, Quebec, Canada)

**Background:** Juvenile myoclonic epilepsy (JME) is a common type of idiopathic generalised epilepsy and is distinctively characterized by myoclonic jerks often associated to generalised tonic-clonic seizures (GTCS) and typical absence seizures. EEG asymmetries are not uncommon in JME and can contribute to the misdiagnosis of this syndrome. The objective of this study is to further characterize patients with focal electroencephalographic abnormalities and specifically in term of response to treatment.

**Methods:** We retrospectively revised clinical and EEG data of a group of consecutive JME patients followed at our Epilepsy Service. The first EEG available for each patient was reviewed by two independent electroencephalographers.

**Results:** Twenty-eight patients with JME were identified: 11 (39.3%) were resistant to at least one anti-epileptic drug (AED), including valproic acid, lamotrigine, topiramate or levetiracetam. All patients except two had generalised epileptiform abnormalities. In our group, EEG asymmetries were detected in 57.1% of the cases. In the AED-resistant group, 63.6% had asymmetries versus 52.9% in the AED-sensitive group but the difference was not statistically significant. Concordance between examiners was good. Analysis of patients with and without asymmetries showed no statistically significant differences in comparisons of age, familial history of seizure, presence of polyspike and slow wave, photosensitivity and timing of EEG related to onset of treatment.

**Conclusion:** Focal electroencephalographic abnormalities are frequent in patients with JME. These features should not be misinterpreted as being indicative of partial epilepsy. In our group, asymmetries were not associated with resistance to treatment.

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### 4. Local field potential synchrony in the amygdalo–hippocampal network during kainate-induced seizures—M. Lévesque<sup>1</sup>, P. Lema<sup>1</sup>, J.M.P. Langlois<sup>2</sup>, R. Courtemanche<sup>3</sup>, L. Carmant<sup>1</sup> (<sup>1</sup>Centre de recherche de l'hôpital Sainte-Justine, CHU Sainte Justine, Montréal, Que., Canada, <sup>2</sup>Département de génie informatique et génie logiciel, École Polytechnique, Montréal, Que., Canada, <sup>3</sup>Department of Exercise Science, Concordia University, Montréal, Que., Canada)

The kainic acid (KA) model is a widely used model to study the pathophysiological mechanisms underlying epileptic seizures. When administered locally or systemically, KA induces epileptiform EEG discharges, repetitive seizures and neuronal lesions that are similar to those seen in human temporal lobe epilepsy. However, very few studies have explored *in vivo* the relation between the activity of local field potentials in different brain structures during KA-induced seizures. In this study, we have explored in Sprague–Dawley rats the local field potential synchrony of the hippocampus and the amygdala during ictal and inter-ictal periods, using multi-channel electrophysiological tech-

niques. Rats were implanted with a headstage composed of five to eight tungsten electrodes (0.5–2.5 M $\Omega$ , 75  $\mu$ m) that targeted either the dorsal hippocampus or the amygdala. Following a recovery period, they were given a single systemic dose of KA (6 mg/kg, *i.p.*) and LFP (1–475 Hz) activity was recorded over a two-hour long period following the injection. Seizures were identified by means of a custom-built automated algorithm and coherence of neural oscillations was measured during control, pre-ictal, ictal and post-ictal periods. We observed a significant increase of coherence in the gamma frequency band (20–80 Hz) during the pre-ictal and ictal periods across amygdalo–hippocampal LFP pairs. These results demonstrate a direct relationship of activities in the amygdalo–hippocampal network during seizures and suggest that gamma oscillations may play a role in the synchronization of spatially segregated neurons.

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### 5. Are cortical tubers epileptogenic? Evidence from electrocorticography—Philippe Major<sup>1</sup>, Sonja Rakowski<sup>1</sup>, Mirela V. Simon<sup>1</sup>, Ming L. Cheng<sup>2</sup>, Emad Eskandar<sup>2</sup>, Joshua Baron<sup>1</sup>, Beth A. Leeman<sup>1</sup>, Matthew P. Frosch<sup>3</sup>, Elizabeth A. Thiele<sup>1</sup> (<sup>1</sup>Department of Neurology, Massachusetts General Hospital, Harvard University, Boston, MA, USA, <sup>2</sup>Department of Neurosurgery, Massachusetts General Hospital, Harvard University, Boston, MA, USA, <sup>3</sup>Department of Pathology, Massachusetts General Hospital, Harvard University, Boston, MA, USA)

**Purpose:** Characterize the epileptogenicity of tubers and surrounding cortex in patients with tuberous sclerosis complex (TSC).

**Methods:** Three pediatric patients with TSC and intractable epilepsy underwent surgical resection of cortical tubers associated with epileptogenic foci. In all patients, pre-surgical imaging revealed a prominent tuber that correlated on EEG with frequent interictal epileptiform discharges and electrographic seizures. Intracranial electrocorticography was performed using subdural grids placed over the tuber and surrounding cortex and depth electrodes positioned directly within the tuber.

**Results:** In all three patients, the depth electrode within the tuber was electrographically silent, while the surrounding cortical tissue showed significant epileptiform activity. The tuber and the electrically active adjacent cortex were resected. The patients experienced a drastic reduction in seizure frequency post-surgery; two were completely seizure-free.

**Conclusions:** Epileptogenicity of cortical tubers may derive not from the lesion itself, but rather from the perturbation or abnormal development of the surrounding cortex. These cases also reinforce that resection of the tuber and the associated epileptogenic cortex can yield effective seizure control.

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### 6. Mechanisms of the ketogenic diet's efficacy in succinic semialdehyde dehydrogenase deficiency—Kirk Nylen<sup>1,2,6</sup>, Sergei Likhodii<sup>4,6</sup>, Jose Luis Perez Velasquez<sup>1,3,6</sup>, W.M. Burnham<sup>2,6</sup>, K. Michael Gibson<sup>5</sup>, O. Carter Snead<sup>1,2,3,6</sup>

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Succinic semialdehyde dehydrogenase (SSADH; ALDH5A1) deficiency (SSADH-d) results in a non-specific neurological disorder that includes significant psychomotor retardation, seizures, behavioral abnormalities and ataxia. There remains no effective treatment for this disorder. A mouse model of SSADH-d (the *Aldh5a1*−/− mouse) has been developed to study the treatment and pathophysiology of this disorder. *Aldh5a1*−/− mice show high levels of ataxia and have a severe seizure disorder where all untreated mice succumb to lethal status epilepticus around post-natal day 20. Recently, we showed that the ketogenic diet (KD) significantly improves the overall phenotype of *Aldh5a1*−/− mice. KD fed *Aldh5a1*−/− mice lived more than 300% longer, showed significantly less ataxia and had improved weight gain when compared to control diet (CD) fed *Aldh5a1*−/− mice. To explore the mechanisms of this effect we performed EEG studies, analyzed serum levels of glucose, beta-hydroxybutyrate (BHB) and free fatty acid levels and we assessed mitochondria profiles using electron microscopy. CD fed *Aldh5a1*−/− mice showed several EEG abnormalities, many which coincided with convulsive behavior. KD fed mice showed remarkable normalization of EEG and had significantly fewer convulsions. These findings are consistent with other studies that have found EEG improvements in KD fed rats and KD fed patients. Study of serum analytes revealed significant elevations in BHB but no significant change in serum glucose or free fatty acids. Ratios of free fatty acids to BHB suggest that *Aldh5a1*−/− mice are oxidizing fatty acids more readily than wild-type mice. Electron microscopy revealed that hippocampal pyramidal cells from KD fed mutants had a significantly higher density of mitochondria than those from CD fed wild-type mice (25% increase), but not from CD fed mutants (15% increase). This is consistent with previous reports showing that the KD is associated with a significant increase in mitochondrial number. Taken together, our data show that the KD normalizes the EEG of *Aldh5a1*−/− mice. Increased ketosis and the subsequent changes in neural energy metabolism caused by increases in the number of mitochondria likely play a critical role in this process.

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**7. Vigabatrin as first line therapy for Infantile Spasms (IS): results of the first six months of the Canadian Paediatric Epilepsy Network (CPEN) neuroprotective is study—Milagros Salas-Prato<sup>1</sup>, Catherine H. Sauerwein<sup>1</sup>, Devendra Amre<sup>2</sup>, Shelly Weiss<sup>3</sup>, Elizabeth Donner<sup>3</sup>, Kevin Farrell<sup>4</sup>, Sharon Whiting<sup>5</sup>, Joseph Dooley<sup>6</sup>, Elaine Wirrell<sup>7</sup>, Gabriel Ronen<sup>8</sup>, Maryse Lassonde<sup>9</sup>, Patricia Giroux<sup>1</sup>, George Karvelas<sup>10</sup>, Lionel Carmant<sup>1</sup> (<sup>1</sup>Research Centre and Division of Neurology, Centre hospitalier universitaire (CHU) Sainte-Justine, Que., Canada, <sup>2</sup>Department of Social and**

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**Background:** Infantile spasms (IS) is a “catastrophic” childhood epilepsy. The goal of this study was to evaluate the efficacy of vigabatrin (VGB) as the treatment (Trt.) of first intention for controlling IS and hypsarrhythmia.

**Methods:** In a multi-centre Canadian double-blind randomized control trial, sixty nine patients with de novo diagnosis of IS were recruited. The patients received VGB as first intention Trt. and if spasms or hypsarrhythmia persisted at week 2, they were administered high doses of ACTH. Children with persistent spasms at week 4, were administered topiramate (TPX). To evaluate Trt. response, seizure logs and video-EEG recordings were obtained at 2, 4, and 24 weeks.

**Results:** A population of 47 male/22 female infants with de novo IS were included. Mean age at diagnosis was 6.7±2.8 months. There were 28 cryptogenic cases, 12 vascular, 7 atrophic, 9 dysplastic, 5 tuberous sclerosis, 4 metabolic, 2 infectious and 1 shaken baby syndrome. Number of responders to VGB, ACTH, TPX, as well as of non-responders to the three Trt. were: cryptogenic (18, 9, 0, 1), vascular (3, 7, 1, 1), atrophic (1, 5, 1, 0), dysplastic (7, 1, 1, 0), tuberous sclerosis (5, 0, 0, 0), metabolic (2, 2, 0, 0), infectious (1, 0, 0, 1) and shaken baby syndrome (1, 0, 0, 0). There was a total of 33 (5 serious), 70 (22 serious) and 6 (not serious) adverse events for each of the above Trt. groups, respectively. This corresponded to an average of 0.48, 2.3 and 1 AE/patient, 96% and 71% of patients being spasm- and seizure-free at 6 months.

**Conclusions:** Contrary to some recent studies, for most children, VGB is highly effective and safe as first line Trt. Children with a vascular aetiology may require ACTH immediately following diagnosis, particularly, if we were to demonstrate that delay in controlling spasms plays a pivotal role in affecting cognitive development.

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**8. The neuroendocrine system in brain injury: A road less travelled?—Michael Sumner<sup>1</sup>, Paul Hwang<sup>2,3</sup> (<sup>1</sup>Rothbart Centre, Ont., Canada, <sup>2</sup>North York General Hospital, Ont., Canada, <sup>3</sup>University of Toronto Epilepsy Research Program, Ont., Canada)**

Higher brain structures (medial temporal, orbitofrontal cortex, insula, brainstem and cerebellum) affect the functions of the hypothalamus. Although relatively well protected except in severe brain injuries, the posterior pituitary (neurohypophysis) often releases

oxytocin and vasopressin. These can produce the SIADH. These neurohormones are very important in pair bonding, and in marital relationship which is frequently disrupted after brain injury.

The anterior pituitary (adenohypophysis) is well protected anatomically but damage to the stalk may disrupt releasing factors, or damage the blood supply. The most lateral portions of the AP are most likely to be damaged, involving release of sex hormones and growth hormone. Inadequate sex hormone levels can impede neuronal and astrocytic recovery from anoxia. Inadequate growth hormone can have detrimental metabolic effects, but is difficult to measure and monitor. Thyroid function and the hypothalamic-pituitary-adrenocortical axis need to be monitored as low cortisone can be life threatening.

The neuroendocrine system can be affected by drug therapy. The opioids depress the endocrine system. The adrenergic agents used to treat apathy and improve frontal system function impede production of prolactin. The blockage of serotonergic neurons by SSRI can increase prolactin release.

Knowledge of the therapeutic and neuroprotective effects of the sex hormones is expanding. An endogenous hormonal system in the brain has neuroreceptors for these neurosteroids. These hormonal perturbations can increase or decrease the likelihood of epilepsy. Neuroendocrine functions need close monitoring after brain injury by specialists operating in a closely-knit team to optimize patient care. A case will be discussed.

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**9. Assessing biochemical and behavioral toxicity of omega-3 polyunsaturated fatty acids at anticonvulsant doses—Ameer Y. Taha<sup>1,2</sup>, Solmaz Alizadeh<sup>1</sup>, Qiudi H. Zeng<sup>1</sup>,**

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Omega-3 polyunsaturated fatty acids (n-3 PUFA), derived from flaxseed and marine fish oils, have been demonstrated to have anticonvulsant properties in animal seizure models. Current anticonvulsant medications that are used to treat seizures have several side-effects, including increased oxidative stress, activation of xenobiotic enzymes, weight gain and sedation. Little is known, however, about the biochemical and behavioural side-effects of n-3 PUFA at anticonvulsant doses. Two experiments were conducted in order to assess biochemical and behavioural toxicity of n-3 PUFA. In experiment 1, we assessed the effects of  $\alpha$ -linolenic acid, which is a precursor to the end product of the n-3 PUFA synthesis pathway, docosahexaenoic acid (DHA), on liver expression of antioxidant and phase II xenobiotic enzymes, as well as lipid composition of liver. In experiment 2, we assessed the effects of DHA on ataxia, sedation, food intake and body weight gain. The results indicate that  $\alpha$ -linolenic acid administration did not increase antioxidant and phase II xenobiotic enzyme mRNA expression, and favourably altered lipid composition of liver. DHA administration at anticonvulsant doses resulted in mild ataxia and sedation, but did not alter food intake or body weight gain relative to controls not receiving the DHA. These findings demonstrate that n-3 PUFA at anticonvulsant doses, improve liver lipid composition, and do not adversely affect biochemical and behavioural measures of toxicity, as seen with conventional anticonvulsant medications.

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