



## Society Proceedings

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### 1. The anticonvulsant effects of docosahexaenoic acid in rodents—Marc-Olivier Trepanier, McIntyre Burnham (University of Toronto Epilepsy Research Program, Canada)

Docosahexaenoic acid (DHA) in an omega 3 polyunsaturated acid with reported anticonvulsant properties. Like phenytoin and carbamazepine it is thought to temporarily stabilize voltage-dependent sodium channels in their inactivated state.

Past reports from other groups have reported dramatic suppression of seizures in animal seizure models by DHA. We have not been able to replicate those *dramatic* anticonvulsant effects in our own studies. We have, however, been able to demonstrate moderate elevations of seizure threshold in chronic, subchronic and acute experiments.

Of interest is the fact that the threshold rises occur almost immediately in acute studies, but take 3+ months to appear in studies where DHA is used as a dietary supplement. We believe that the delayed effects of DHA in dietary studies may relate to the complex pharmacokinetics of DHA following oral administration.

The fact that dietary DHA is slow to act may explain the failure of experimenters to find antiseizure effects in some of the shorter clinical and animal trials.

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### 2. The origin of primary bilaterally synchrony of H. Jasper, P. Gloor seen in generalized epilepsy and the secondary bilaterally synchrony of W. Blume seen in secondary generalized epilepsy—I. Park, P. Hwang (University of Toronto Epilepsy Research Program, Canada)

In their landmark research published in the 1950s W. Penfield and H. Jasper proposed the “centrencephalic” hypothesis proposing that “a primarily subcortical, upper brainstem and/or thalamic system with bilaterally diffuse cortical projections within which the epileptic discharge is generalized and spread<sup>1</sup>” was the origin of primary generalized seizures with primary generalized bilaterally synchronous (PBS) discharges seen on the EEG.

P. Gloor further developed on this theory and the “cortical” hypothesis of Gibbs and Gibbs and based on his clinical research of intracarotid injections of sodium amytal and metrazol in epileptic

patients and the feline penicillin model proposed a “cortico-reticular” hypothesis for the above. Thus emphasizing the important role the cortex plays in PBS.

W. Blume’s paper published in the Canadian Journal of Neurological Sciences (October 2, 2001), he described the concept of secondary bilateral synchrony, which he refers to a focal spike or sharp waves leading directly to “bilaterally synchronous epileptiform paroxysms.” Thus stating that the above EEG phenomenon can also be seen in patients suffering from secondary generalized seizures and may point towards a specific epileptogenic zone in the brain.

This paper will aim to review the opinions of three master pioneer electro-encephalographers. The origins of primary bilateral synchrony proposed by H. Jasper and P. Gloor and the secondary bilateral synchrony (SBS) of W. Blume.

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### 3. Gamma knife surgery in hypothalamic hamartoma: An effective treatment of refractory epilepsy with good outcome on quality of life and cognition—Pascale Bourgeois, David Mathieu, Julie Duval, Charles Deacon (Division of Neurosurgery, Université de Sherbrooke, Centre Hospitalier Universitaire de Sherbrooke, Canada)

**Rationale:** Hypothalamic hamartomas (HHs) are intrinsically epileptogenic congenital lesions typically presenting with drug resistant epilepsy. Patients affected also suffer from progressive cognitive deficits. Based upon previous studies, Gamma-knife surgery for HHs seems to be effective regarding epilepsy outcome with minimal side effects. Little data is available on the neurocognitive effect of this procedure. At the Centre Hospitalier Universitaire de Sherbrooke, we have undertaken a prospective observational study of patients who underwent radiosurgery for HHs, evaluating the response rate of seizures and the impact on cognition and quality of life.

**Methods:** Patients were included in the study if they had an HH, refractory epilepsy, and no other suspected seizure focus. After radiosurgery, seizure status was assessed every three months and reported using the Engel Classification. Neuropsychological evaluation and quality of life evaluation using a standardized questionnaire (QOLIE-89) was performed at baseline and annually thereafter.

<sup>1</sup> Gloor P. Generalized cortico-reticular epilepsies. *Epilepsia* 1968;9:249–62.

**Results:** Twelve patients with refractory epilepsy have been included so far in the study. Age ranged from 14 to 57 years. Margin doses ranged from 14 to 20 Gy. Nine patients had smaller hamartomas (Régis classification Grade I–III) and underwent treatment of the entire lesion. Three patients had larger lesions (Grade IV–VI) for which a radiosurgical disconnection was attempted. One of them had a second treatment with full lesion coverage. Among the seven patients treated with full lesion coverage with more than two years of follow-up, five (70%) are seizure free (Engel I). One patient has only rare seizure (Engel II), and one did not improve (Engel IV). Mean time to seizure freedom was twelve months (range 4–22). Disconnection led to no or little improvement in epilepsy (Engel IV in two patients and Engel IIIa in one). Nine patients had an abnormal cognitive profile at baseline. Four of them had a second evaluation after two years, and marked improvement in multiple domains of cognition occurred in three patients, and one remained stable. We observed a tendency toward improvement of quality of life evaluated with QOLIE-89, with a median result of 53% before treatment compared to 84% one or two years after treatment ( $p = 0.068$ ). Three patients had transient psychiatric disturbances after treatment (major depression with psychotic features requiring hospitalization in two, and impulsive behavior in one).

**Conclusions:** In this prospective study of patients with refractory epilepsy associated with HHS, radiosurgery was effective in most patients when the entire lesion could be targeted. Some encouraging effects were also observed for cognition and quality of life, but this needs to be further evaluated in larger series of patients. Radiosurgical disconnection of large lesions was ineffective. Psychiatric disturbances as a possible side effect of this procedure need to be investigated further. For small HHS, radiosurgery with full lesion coverage should be a first line surgical therapy.

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#### 4. ICU EEG study—Omar Khan, Christina Azevedo, Justin Montanye, Juan Gonzalez, Syed Arshad, Mark Natola, Stephen Surgenor, Richard Morse, Richard Nordgren, Krzysztof Bujarski, Gregory Holmes, Barbara Jobst, Vijay Thadani (Department of Neurology, Dartmouth Hitchcock Medical Center, NH, Lebanon)

**Introduction:** Prolonged EEG monitoring in the ICU is now common. Studies suggest that the prevalence of seizures and nonconvulsive status epilepticus (NCSE) is 10% or more. However, the selection criteria for monitoring remain ambiguous, and the impact of prolonged EEG monitoring on treatment is unclear. We addressed these questions by performing prolonged EEG on patients for whom a routine 30-min or prolonged EEG was requested by ICU staff.

**Methods:** During a prospective but not randomized 22-month study, EEGs were requested by ICU staff on 130 patients, with diagnoses of trauma, tumor, stroke, metabolic derangement, cerebral hemorrhage, and hypoxic–ischemic injury. Patients were placed in three groups.

**Group 1:** 34 patients received a 30-min EEG, because for various reasons long-term recording could not be done.

**Group 2:** 83 patients for whom staff requested a 30-min EEG, instead received 16–24 h of continuous video-EEG monitoring.

**Group 3:** 13 patients, with known epilepsy, for whom continuous video-EEG monitoring was requested, received 16–24 h of recording to monitor suspected status epilepticus.

Epileptologists compared the first 30 min of EEG with the subsequent recording to see if any additional information was obtained, and if it impacted treatment.

**Results:** **Group 1:** 34 patients had a routine 30-min EEG. One was normal, 27 were slow or poorly reactive, and six (18%) showed epileptiform activity, including one with electrographic seizures. **Group 2:** 83 patients were monitored with video-EEG for 16–24 h. All EEGs were abnormal with slowing and poor reactivity. 28/83 patients (34%) showed epileptiform findings in the first 30 min, including periodic epileptiform discharges (PEDs), generalized or focal epileptiform discharges, burst suppression, triphasic waves, and 2 patients had clinical seizures. 5/28 developed additional epileptiform changes overnight, including two more with clinical seizures. 55/83 patients (66%) had no epileptiform findings in the first 30 min, but 7/55 developed these overnight, including two with electrographic and one with clinical seizures. Overall, in 12/83 patients additional epileptiform abnormalities developed overnight, and in 7/83 treatment was changed based on prolonged as opposed to routine EEG. 3/7 patients in whom treatment was changed showed improvement. **Group 3:** 13 patients known to have epilepsy, who presented with seizures, were deliberately placed on long term video-EEG monitor. 9/13 (69%) showed epileptiform abnormalities in the first 30 min including three with NCSE and one with focal seizures. Overnight two more evolved into NCSE, and prolonged EEG influenced therapy in 6/13.

**Discussion:** In 83 unselected ICU patients, overnight video-EEG, as opposed to a 30-min EEG, detected additional epileptiform abnormalities in 12 patients (14%), and 7/83 patients (8%) had changes in treatment based on findings from prolonged as opposed to routine EEG. In contrast, patients with epilepsy who presented with seizures were more likely than other ICU patients to have NCSE, and prolonged EEG influenced treatment in 6/13 (46%).

This study suggests that long-term EEG monitoring in an unselected ICU population rarely influences treatment or outcome. In a selected population with known epilepsy the benefit may be larger.

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#### 5. Sleep disturbances in Prader-Willi syndrome and the effects of topiramate and modafinil—Lauren Hall, Colin Shapiro, Glenn Berall, Paul Hwang (University of Lethbridge, Youthdale Sleep Lab, North York General Hospital, UTERP, University of Toronto, Ont., Canada M2K 2W2)

**Aim:** Prader-Willi Syndrome (PWS) is a condition resulting from abnormalities on chromosome 15, which is thought to affect hypothalamic and pituitary function. PWS is characterized by an excessive appetite, hyperphagia, decreased basal metabolic rate and obesity post-infancy. Sleep disorders and excessive daytime sleepiness have also been reported in PWS.

**Methods:** In this retrospective study, various demographic and sleep parameters of PWS subjects were collected and analyzed to determine if topiramate (TPM) or modafinil (MD) have an effect on sleep in this population. Subjects with a PWS diagnosis had polysomnography and multiple sleep latency test (MSLT) completed using a 36-channel EEG system.

**Results:** The subjects were placed into three groups: individuals not prescribed TPM or MD were PWS controls ( $n = 25$ ); individuals prescribed TPM ( $n = 4$ ); and individuals prescribed MD ( $n = 1$ ). All subjects were also following the Red–Yellow–Green (RYG) diet. The age, body mass index, mean sleep efficiency, mean sleep latency, mean REM sleep onset, mean apnea/hypopnea index, sleep stage percentages, mean MSLT sleep latency, and MSLT REM sleep disturbances were analyzed. A significant increase ( $p = .037$ ) in REM sleep onset was found in the TPM group when compared to the PWS controls. When compared to age-matched controls, both the TPM and PWS control group had significant increases in wakefulness ( $p = .018$  and  $p = .001$ , respectively) and significant decreases in REM sleep percentage ( $p = .031$  and  $p = .001$ , respectively).

**Conclusion:** These sleep disturbances and impact on BMI should be considered in the management of young persons with PWS, including the use of RYG diet, and TPM or MD.

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## 6. Neuroplasticity, epilepsy and neuroplasticity as a potential treatment for some forms of epilepsy—Michael G. Sumner, Paul A. Hwang (North York General Hospital, Departments of Pediatrics and Medicine, University of Toronto, Epilepsy Research Program and Ontario Brain Institute, Canada)

Neuroplasticity is the panacea of neuropsychiatry, changing ‘bad behaviour’ patterns and experiences into ‘good behaviour’ patterns and people will then ‘live happily ever after’ i.e., Pollyanna however, to paraphrase Star Wars, there is always ‘the dark side’ of neuroplasticity: including epilepsy, addiction, chronic pain, allodynia and complex regional pain syndromes. Neuroplasticity is being explored extensively to promotive recovery from brain trauma, spinal injury.

**Aim:** This is a brief review of the literature in neuroplasticity of epilepsy and psychiatry and the discussion of the neurobehavioral treatment of epilepsy.

**Method:** Case presentation of two patients: John Doe and Richard Roe, one of whom has been extensively investigated at numerous first rate neurological institutions, and the second who has been also extensively investigated. They will both be treated with a variant of the Andrews-Reiter approach. John Doe has three epileptiform foci: two in the left frontal and temporal regions and one in the right temporal region. Richard Roe had a significant head trauma and a 3D SPECT scan showing significant hypoperfusion of the temporal lobes and prefrontal cortex but over-activity in the thalami and basal ganglia. He has frequent intractable panic attacks whose symptoms overlap with those of complex partial seizures despite a negative workup. Both patients have been thoroughly evaluated by a competent neurologist/epileptologist and a neuropsychiatrist.

**Results:** The response of either patient to therapy using this approach is not yet known. They are being treated with the usual pharmacological AEDs.

**Conclusion:** Neuroplasticity is a major phenomenon in neuroscience. How effective the Andrews Reiter approach will be in these two subjects is not yet known but certainly neuroplasticity and neurogenesis is a major field of investigation.

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## 7. Clinical and EEG features of action myoclonus–renal failure syndrome—Dina Amrom<sup>a,b</sup>, Martin Veilleux<sup>b,d</sup>, Leanne M. Dibbens<sup>f</sup>, Samuel F. Berkovic<sup>g</sup>, Frederick Andermann<sup>b,d,e</sup>, Eva Andermann<sup>a,b,c</sup> (<sup>a</sup>Neurogenetics Unit, Montreal Neurological Hospital and Institute, Canada, <sup>b</sup>Dept. of Neurology & Neurosurgery, McGill University, Montreal, Canada, <sup>c</sup>Human Genetics, McGill University, Montreal, Canada, <sup>d</sup>Epilepsy Service, Montreal Neurological Hospital and Institute, Canada, <sup>e</sup>Pediatrics, McGill University, Montreal, Canada, <sup>f</sup>Epilepsy Research Program, School of Pharmacy and Medical Sciences P4-47, University of South Australia 5000, Australia, <sup>g</sup>Epilepsy Research Center, Department of Medicine (Neurology), University of Melbourne, Austin Health, Heidelberg, Melbourne, Australia)

**Background:** Action myoclonus renal failure (AMRF) syndrome is an autosomal recessive form of progressive myoclonus epilepsy with tremor and myoclonus that may be intractable. It was initially described in three French Canadian families. AMRF is caused by

mutations in the *SCARB2* gene, encoding a lysosomal membrane protein. Disease onset is usually in the late teens or early twenties, and begins with tremor and proteinuria, progressing to action myoclonus, tonic–clonic seizures and renal failure.

**Methods:** We describe the clinical and EEG investigations, including EEG with surface EMG electrodes (EEG-sEMG), as well as clinical video recording in three patients with AMRF syndrome associated with a confirmed *SCARB2* gene mutation.

**Results:** Patients 1 and 2 had onset of action myoclonus at 21 and 22 years, respectively. They had no proteinuria. EEG-sEMG in both patients showed a normal background activity with numerous trains of generalized polyspike and waves at a frequency of 4 Hz, at times associated with jerks. In patient 1 there was photosensitivity at lower stimulation frequencies (2–6 Hz) and one generalized tonic–clonic seizure was recorded at 8 Hz lasting 1 min.

Patient 3 presented fine tremor of upper limbs at 14 years, renal failure at 15 years, and action myoclonus at 27 years. He never had tonic–clonic seizures. The EEG-sEMG showed a tremor that had a frequency of 4–5 Hz, there were no myoclonic jerks demonstrated on surface electrodes. All three patients had normal intelligence and the *SCARB2* nonsense mutation Q288X.

**Discussion:** The early clinical findings in AMRF are fine tremor and proteinuria, followed by action myoclonus, renal failure and occasional generalized tonic–clonic seizures. In some patients, the renal failure may present prior to the neurological symptoms or may not develop.

The key EEG findings consist of background activity within the normal range, unlike many PME’s, where it is slow. The other EEG findings are similar to those seen in other PME’s, in particular the photosensitivity at low stimulation frequencies.

In the early stages of the disease, JME should be in the differential diagnosis. If the tremor and myoclonus become intractable, and/or the patient develops proteinuria or renal failure, AMRF should be considered.

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## 8. Transition into and out of a seizure in the hippocampal CA3 region: A failure of presynaptic release—P.L. Carlen, Z.J. Zhang, J. Koifman, D.S. Shin, H. Ye, C.M. Florez, L. Zhang, T.A. Valiante (Division of Fundamental Neurobiology, Toronto Western Research Institute, Toronto Western Hospital, Canada)

How the brain transitions into and out of a seizure is mysterious. Using the intact mouse hippocampus preparation, recurrent seizure-like events (SLEs) in low  $Mg^{2+}$ /high  $K^+$  perfusate were measured in the CA3 region. The SLE was characterized by a “preictal phase”, which abruptly turns into a higher frequency “ictal” phase. Blockade of  $GABA_A$  receptors shortened the preictal phase, abolished interictal bursts, attenuated the slow preictal depolarization, but with no effect on the ictal duration. On the other hand, SLEs were blocked by glutamate receptor blockade. In CA3 pyramidal cells and stratum oriens non-fast and fast spiking interneurons, recurrent  $GABA_A$  inhibitory postsynaptic currents (IPSCs) predominated interictally and during the early preictal phase, synchronous with extracellularly measured recurrent field potentials (FPs). These IPSCs then decreased to zero or reversed polarity by the onset of the higher frequency ictus. However postsynaptic muscimol-evoked  $GABA_A$  responses remained intact. Simultaneously, excitatory postsynaptic currents (EPSCs) synchronous with the FPs, markedly increased to a maximum at the ictal onset. The reversal potential of the compound postsynaptic currents (combined simultaneous EPSCs and IPSCs: PSCs) became markedly depolarized during the preictal phase, whereas the muscimol-evoked  $GABA_A$  reversal potential remained unchanged. During the late preictal phase, interneuronal excitability

was high, but IPSCs, evoked by local stimulation, or osmotically by hypertonic sucrose application, were diminished, disappearing at the ictal onset. EPSCs evoked by hypertonic sucrose application, were maximal at ictal onset, disappearing at the end of the ictus. We conclude that the interictal and early preictal states are dominated by GABAergic activity, with the onset of the ictus heralded by exhaustion of presynaptic release of GABA, and unopposed increased glutamatergic responses. The ictus stops when presynaptic release of glutamate is exhausted.

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**9. Phenotypic variability in Mabry syndrome: Hyperphosphatasia with seizures and neurologic deficit—Miles D. Thompson<sup>a</sup>, Frances J. Sharom<sup>b</sup>, John A. Phillips<sup>c</sup>, Peter N. Robinson<sup>d</sup>, David E.C. Cole<sup>e</sup>, Danielle M. Andrade<sup>f</sup> (<sup>a</sup>Department of Pharmacology, University of Toronto, Toronto, Ont., Canada, <sup>b</sup>Department of Molecular and Cellular Biology, University of Guelph, Guelph, Ont., Canada, <sup>c</sup>Division of Medical Genetics & Genomic Medicine, Medical Center North, Vanderbilt University School of Medicine, TN, USA, <sup>d</sup>Institut für Medizinische Genetik und Humangenetik, Charité-Universitätsmedizin Berlin, Berlin, Germany, <sup>e</sup>Department of Clinical Pathology, Sunnybrook & Women's College Health Sciences Centre, Toronto, Ont., Canada, <sup>f</sup>Toronto Western Hospital, Krembil Neuroscience Centre, Epilepsy Genetics Program Division of Neurology, University of Toronto, Toronto, Ont., Canada)**

Hyperphosphatasia with neurologic deficit (Mabry syndrome) was first described in a single family (OMIM#239300) by Mabry et al. (1970). Although considered rare at the time, more than 20 individuals with the triad of developmental disability, seizures, and hyperphosphatasia have been identified world-wide. The 1–6 mannosyltransferase 2, phosphatidylinositol glycan V (*PIGV*) gene

has been found to be disrupted in some patients with the additional feature of brachytelephalangy. To date, approximately 50% of these patients have been identified to be either homozygous or compound homozygous for *PIGV* mutations. Here we present four cases with *PIGV* mutations. Two siblings were found to be compound heterozygotes for c.467G>A and c.494C>A in exon 3 of *PIGV* (the c.494C>A *PIGV* variant is novel). A third patient with similar phenotype, was a compound heterozygote for the known c.1022C>A/c.1022C>(p.Ala341Glu/p.Ala341Val) mutation. This patient was also noted to have lysosomal storage in cultured fibroblasts – a feature present in approximately half of known cases – both *PIGV* positive and negative. In contrast, the fourth patient who had no apparent hand abnormality, was found to be heterozygous for a previously unclassified c.1369C>T mutation in exon 4 of the *PIGV* gene, resulting in a p.Leu457Phe substitution in the catalytic domain of the enzyme. Unless this variant has a dominant negative effect, however, it seems likely that another GPI biosynthesis gene variant may contribute to the disorder, possibly through digenic inheritance. Since half of these cases (Thompson et al., 2010, 2012) have *PIGV* mutations, we suggest that other genes critical to GPI anchor biosynthesis are likely to be disrupted in some patients.

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