Does early-life stress play a role in epileptogenesis during development—P. Lema, K. Bibeau, M. Salas-Prato, M. Brochu, L. Carmant (Centre de Recherche, CHU Ste-Justine, University of Montreal, Montreal, PQ, Canada)

**Background:** In his book, Fyodor Dostoevsky clearly described the role of stress as a precipitating factor of his first seizure. In our epilepsy clinics, patients often link increased seizure frequency with periods of stress. Although there is a role of stress in ictogenesis, we wanted to explore the possibility that early life stress could be implicated in epileptogenesis.

**Methods:** In our recently developed animal model of dual pathology, we observed that 90% of animals with congenital brain malformation developed epilepsy following prolonged febrile seizures. We also observed that most of the epilepsy resistant animals were females. To assess the role of stress in our model, we measured corticosterone levels at P1 before and after lesioning the newborn rat and at P10 before and after the prolonged febrile seizures in rats and compared the results between rats who develop epilepsy versus those who did not.

**Results:** In the animals that become epileptic, there is a significant rise of corticosterone when comparing levels prior and after the induction of the lesion (+36%). In comparison, this rise in stress hormones is not seen in pups that do not develop epilepsy (−28%). In contrast, at P10, in the hyporeactive period both groups show a significant rise in corticosterone levels.

**Discussion:** Our results support the hypothesis that early life stress may increase the propensity of developing epilepsy following a second insult in later life. However, further studies are required to confirm this in our model and to determine if early life stress alone is sufficient to be the first-hit in our two-hit model of epileptogenesis.

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Identifying EEG features of nonconvulsive status epilepticus (NCSE)—Ji Soo Choi, Gregory Krauss, Peter Kaplan (Johns Hopkins School of Medicine, Baltimore, MD, USA)

The EEG features of NCSE are controversial. Readers may use a number of EEG domains – discharge-complex morphology, frequency, rhythmicity/evolution and focality to conclude whether a particular record shows NCSE, or conversely, for example, an encephalopathy. The choice, grading and prioritization of these features have not been formalized. Two readers independently classified 43 NCSE EEG recordings into four NCSE-probability grades: severe (grade 4); moderate (grade 3); mild (grade 2) and possible/borderline (grade 1). They then measured the frequency, rhythmicity, morphology and focality of recordings and determined the specificity of these features for determining of the effects of seizure activity on reproductive and feeding systems may lead to the development of novel treatment solutions.

**Methods:** Female Wistar rats were implanted with electrodes aimed at the amygdala. Post-surgery, subjects were weighed weekly and vaginal smears were obtained daily to monitor estrous cyclicity. Kindled subjects were given seizure-inducing electrical stimulation, while sham-kindled subjects were handled similarly but not stimulated. Twenty-four hours after a minimum of 40 generalized seizures, kindled subjects together with yoked controls were sacrificed with brain, serum and ovaries extracted.

**Results:** After approximately 15 generalized seizures, kindled subjects experienced significantly more abnormal estrous cycle days compared to controls. Serum analysis revealed elevated levels of the ovarian hormone estradiol among kindled subjects. After approximately seven generalized seizures, kindled subjects were significantly heavier than controls. Serum analysis revealed significantly higher levels of the long-term satiety hormone leptin among kindled subjects. Correlational analyses reveal that measures of reproductive dysfunction and obesity are significantly related.

**Conclusions:** Seizures originating from the limbic system are sufficient to disrupt multiple hormone systems. Further investigations into the physiological mechanisms responsible for the dysfunctions are required.

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Limbic seizures induce neuroendocrine dysfunction – Implications for reproductive dysfunction and obesity—Kathryn M. Hum, W. McIntyre Burnham (University of Toronto, Epilepsy Research Program Toronto, ON, Canada)

**Introduction:** Individuals with epilepsy often suffer co-morbid dysfunctions that impact quality of life. A better understanding
NCSE grades. Unique patterns of features distinguished patients in all four grades. EEGs for grade 4 records were >2.5 cps, rhythmic and had sharp/spike morphology; grade 3 records were generally less frequent (<2.5) and were either sharp, or rhythmic and nonfocal; grade 2 records were either quasirhythmic, low in frequency (2–2.5 cps) or nonfocal; grade 1 records had frequencies <2 cps. Patients with clinically definite NCSE (e.g. recovery with lorazepam treatment) had grades 4–1.

These findings demonstrate that consistent constellations of EEG features can be used to classify NCSE records. These findings need to be prospectively validated, but may characterize NCSE patterns.

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Examining seizure-induced effects on the dendritic growth of immature neurons, using in vivo time-lapse imaging of the intact juvenile brain—D. Sesath Hewapathirane, Simon Chen, Wesley Yen, Kurt Haas (Brain Research Centre, University of British Columbia, Vancouver, BC, Canada)

Considering that seizures are most common during childhood, understanding the possibly detrimental effects of seizures on neural growth during development is highly warranted. The overall aim of this work is to establish a novel model system to directly examine the effects of seizures on dendritic morphogenesis and synaptogenesis during brain development. The albino Xenopus laevis tadpole is an attractive model organism as it allows for the imaging of neuronal growth and synaptic events, in vivo, in real-time within the intact developing brain. Our initial experiments characterized seizure activity induced following administration of pentylenetetrazol (PTZ) – behaviourally, electrophysiological, and by in vivo imaging of neuronal calcium dynamics. Bath application of 15 mM PTZ to freely swimming or acutely immobilized tadpoles reliably elicited behavioural and electrographic seizure activity with a latency of 10–15 min. We then examined both the immediate and short-term effects of PTZ-induced seizures on dendritic growth in vivo. Repeated (time-lapse) imaging of individual fluorescently labeled neurons over a period of 8 h revealed that prolonged PTZ-induced seizures lead to retraction of the growing dendritic arbor of immature neurons. More rapid imaging – every minute over the course of an hour – revealed that changes in dendritic growth dynamics begin to occur approximately 30 min after seizure induction. Our unique model system circumvents many of the limitations presently hindering research using mammalian models. The strength of this seizure model is the ability to conduct live-imaging (in real-time), in vivo, during a seizure event and, in addition, to examine whether the observed short-term changes are persistent.

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Abnormal neurophysiological findings in MS patients—Kevin Lam 1, Chen Li 2, Jane Shaw 3, Paul A. Hwang 2,4 (1 Queen’s University, Kingston, Canada; 2 Neurophysiology Lab, North York Clinic, Toronto, ON, Canada; 3 The Hospital for Sick Children, Toronto, ON, Canada; 4 University of Toronto Epilepsy Research Program, Toronto, ON, Canada)

Objective: To evaluate visual evoked potentials (VEPs), somatosensory evoked potentials (SEPs), and brainstem auditory evoked potentials (BAEPs) in the diagnosis of multiple sclerosis (MS) in patients on and off interferon therapy.

Background: Since the McDonald criteria of 2001, MRI has become the gold standard in the diagnosis of MS. However, since early diagnosis followed by disease-modifying treatment improves neurological outcome, neurophysiological testing may lead to earlier diagnosis.

Methods: Ten MS patients, five currently on interferon therapy (N1) and five not on interferon therapy (N2) were reviewed. The VEPs, BAEPs, and SEPs (median or posterior tibial nerve stimulation) were analyzed for each patient. The frequency distributions were analyzed for statistical significance.

Results: Ten patients, 9 female and 1 male, mean age 43.7 years, were diagnosed with abnormal MRI findings of MS. In N1, three patients had an abnormal VEP, four patients had an abnormal SEP, and two patients had an abnormal BAEP prior to diagnosis. In N2, four patients had an abnormal VEP, all patients had an abnormal SEP, and two patients had an abnormal BAEP. Altogether, 20/30 abnormal results were obtained: 9 normal tests for N1 and 11 abnormal tests for N2. Of the 20 tests, 7 were abnormal VEPs, 9 were abnormal SEPs, and 4 were abnormal BAEPs. There is significant evidence that abnormal SEPs and VEPs are indicative of MS diagnosis (P < 0.01).

Conclusions: Clinical neurophysiological testing, in particular VEP and SEP, can lead to early diagnosis and treatment of multiple sclerosis both with and without interferon therapy.

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The cellular dynamics of spontaneous transition to seizure: More exciting than you think—Miron Derchansky, Shokrollah S. Jahromi, Mandi Mamani, Damien S. Shin, Atilla Sik, Peter L. Carlen (Toronto Western Research Institute and the University of Toronto Epilepsy Research Program, Toronto, Canada)

The neural mechanisms responsible for spontaneous seizure transition are unresolved. It has been suggested that a shift from inhibitory to excitatory GABAergic drive could underlie this transition. Using the isolated mouse hippocampus perfused with low magnesium ACSF, we investigated the cellular dynamics of seizure transition performing intracellular recordings from pyramidal cells, fast- and non-fast spiking interneurons in the CA1 region. Intracellular signal integration during the transition period to seizure started with dominant inhibitory synaptic input followed by dominant excitation just prior to seizure onset. Efflux of bicarbonate ions through the GABAA receptor did not account for this excitation. GABAergic excitation via reversed IPSPs was also excluded, since somatic and dendritic GABAergic responses to externally applied muscimol remained hyperpolarizing throughout the transition period. In addition, abolishing EPSPs in a single neuron via intracellularly applied QX222, revealed that inhibitory synaptic drive was maintained throughout the entire transition period. We suggest that rather than a shift from inhibitory to excitatory GABAergic drive prior to seizure onset, there is a dynamic change in the interaction between afferent synaptic inhibition and excitation to pyramidal neurons and interneurons of the hippocampus, with
maintained inhibition and increasing, entrained ‘overpowering’ excitation.

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Brain trauma, epilepsy and personality disorder?—Michael Sumner, Paul Hwang (Rothbart Pain Centre, Thornhill, Paediatric Neurology Division, Departments of Paediatrics and Medicine, North York General Hospital, University of Toronto Epilepsy Research Program, Toronto, ON, Canada)

Objective: To determine the clinical, behavioral and EEG changes after traumatic brain injury (TBI) in adolescents and young adults.

Rationale: Damage to the brain, especially the temporal lobes, is associated with a persistent post-concussion syndrome, borderline or sociopathic personality disorder and impulse dyscontrol. An overlap with complex partial seizures of temporal lobe origin is suggested: impaired responsiveness, olfactory hallucinations, déja` vu or jamais

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Objectives: To determine the clinical, behavioral and EEG changes after traumatic brain injury (TBI) in adolescents and young adults.

Rationale: Damage to the brain, especially the temporal lobes, is associated with a persistent post-concussion syndrome, borderline or sociopathic personality disorder and impulse dyscontrol. An overlap with complex partial seizures of temporal lobe origin is suggested: impaired responsiveness, olfactory hallucinations, déja` vu or jamais vu, in ictal or interictal behaviour. We hypothesize that temporal lobe damage results in impaired cognitive functions associated with personality changes and abnormal temporal EEG findings.

A retrospective study of youth (16–35 years of age) after moderate TBI had detailed neurological (PAH) and neuropsychiatric (MS) evaluation independently, and an 18-channel EEG sleep studies with zygomatic electrodes. Antiepilepsy therapy employed the usual AEDs appropriate for the seizure types, with monitoring of blood levels. Neuroimaging with head CT and/or MRI was performed, with attention to medial temporal structures.

Follow up by an experienced team of neurologist/epileptologist (PAH) and neuropsychiatrist (MS) extended from 6 months over 6 years (mean 3 years).

Data were analysed for headaches, seizure control, AEDs and side-effects, attention, behavioural disorders, structural lesions and EEG abnormalities. When available, detailed neuropsychological studies were analyzed with statistical tests of significance (P < 0.05).

Preliminary results suggest clinical features following moderate TBI of temporal lobe dysfunction: verbal and non-verbal memory, learning and amnesic disorders, complex partial seizures, overlapping the borderline personality disorder. These findings suggest limbic dysfunction underlying the behavioral disturbance, EEG and structural changes in medial temporal structures after TBI.

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Succinic semialdehyde dehydrogenase (SSADH; ALDH5A1) deficiency is a disorder that affects GABA degradation and manifests in humans as γ-hydroxybutyric aciduria. SSADH deficiency is characterized by a non-specific neurological disorder that includes significant psychomotor retardation, seizures, behavioral abnormalities and ataxia. There is no adequate treatment currently available. A mouse analog of SSADH deficiency has been developed (Aldh5a1+/−). The Aldh5a1+/− mouse exhibits ataxia, significant developmental delay and a progressive seizure disorder that results uniformly in lethal status epilepticus between post-natal days 25-30. Here we show that a KD is able to rescue the Aldh5a1+/− phenotype by prolonging the lives of mutants by more than 300%. The KD also led to a significant reduction in ataxia and a significant improvement in weight gain. Whole cell voltage clamp recordings of miniature inhibitory post-synaptic currents (mIPSC) revealed that the Aldh5a1+/− mice have significantly attenuated mIPSC activity when compared to controls. We show here that the KD appears to restore mIPSC activity in Aldh5a1+/− subjects. Although the exact mechanism behind this effect remains unclear, we believe this is the first report of the KD affecting mIPSC activity. These data have therapeutic relevance in the treatment of human SSADH deficiency.

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Levetiracetam use for refractory pediatric epileptic syndromes—P. Giroux, M. Salas-Prato, Y. Théoret, L. Carmant (Centre de Recherche, CHU Ste-Justine, University of Montreal, Montreal, PQ, Canada)

Rationale: The first objective of this study is to evaluate the efficacy and tolerability of levetiracetam in add-on therapy in children ages 4–18 years old with refractory epilepsies. The second objective is to determine the value of therapeutic dosage monitoring of levetiracetam in this population.

Methods: In the retrospective part of this study, 75 children followed at the Neurology Clinic of Sainte-Justine Hospital were selected because they were currently treated or have been treated with levetiracetam. Their medical files were reviewed for efficacy and tolerability of the new drug. The prospective part of this study is a pharmacological part in which blood levels were determined by HPLC-UV method and correlated with the given dose per kilo.

Results: Fifty-three files of children between ages of 4 and 19 years of age were kept for the retrospective analysis. There were 23 females and 30 males. Thirteen patients (24.5%) became seizure-free after taking levetiracetam for a period of at least 9 months. The improvement in seizure frequency was calculated with 52 patients. Eight patients (15%) showed no significant improvement (between 0% and 25%), 10 (19%) showed non-significant improvements (between 26% and 50%), 10 (19%) had a significant improvement (between 51% and 75%) and 24 (46%) improved by more than 76%. Fourteen children experienced adverse effects with the more common being increased seizures in two, headaches in two, worsened behavior in three, and drowsiness in five. Five patients stopped medication due to these adverse effects. Levetiracetam seems to be efficient for both partial and generalized epilepsy. The dosage appears to be linear with the dose/kilo for all patients tested.

The ketogenic diet rescues the lethal phenotype and restores synaptic activity in succinic semialdehyde dehydrogenase deficient mice—Kirk Nylen1,2,6, Sergei Likhodii4,6, Jose Luis Perez Velasquez1,2,6, W.M. Burnham2,6, K. Michael Gibson2, O. Carter Snead1,2,3,6 (1 Neuroscience and Mental Health, Hospital for Sick Children, Canada, 2 Department of Pharmacology, University of Toronto, Canada, 3 Division of Neurology, Hospital for Sick Children, Canada, 4 Department of Paediatric Laboratory Medicine, Hospital for Sick Children, Canada, 5 Division of Medical Genetics, Children’s Hospital of Pittsburgh, USA, 6 University of Toronto Epilepsy Research Program, Toronto, ON, Canada)
Enrichment of brain lipids with omega-3 polyunsaturated fatty acids increases resistance to pentylenetetrazol induced seizures—Ameer Y. Taha 1,2, Elvis Filo 1, David W.L. Ma 3, Jing X. Kang 4, W. McIntyre Burnham 1,2 (1 Department of Pharmacology, Faculty of Medicine, University of Toronto, Toronto, Canada, 2 University of Toronto Epilepsy Research Program, Faculty of Medicine, University of Toronto, Toronto, Canada, 3 Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Canada, 4 Department of Medicine, Harvard Medical School, Boston, MA, USA)

Epilepsy is a serious neurological disorder which is characterized by spontaneous, recurrent seizures. Current anticonvulsant medications have side effects including weight gain, fatigue and sedation. Omega-3 (n-3) polyunsaturated fatty acids (PUFA), derived from marine fish oils, have been considered as an alternative treatment for patients with epilepsy. Accordingly, we hypothesized that enrichment of brain lipids with n-3 PUFA, in the form of docosahexaenoic acid (DHA), would inhibit the epileptic-like seizures induced by pentylenetetrazol (PTZ). Two experiments were conducted in order to test the hypothesis. In Experiment 1, we demonstrated that the increased levels of n-3 PUFA, primarily DHA, in brain phospholipids of male and female transgenic Fat-1 mice, which are capable of de novo synthesis of n-3 PUFA from n-6 fatty acids increases resistance to PTZ. In Experiment 2, we showed that intra-peritoneal injection of n-3 PUFA, in the form of docosahexaenoic acid composition in brain, and is associated with increased latency to seizure onset (P < 0.05). These findings indicate that n-3 PUFA have anticonvulsant properties, and would be potentially useful in the treatment of epilepsy.

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Atypical presentations of idiopathic occipital lobe epilepsy—Deepa Sirsi, Srishti Nangia, Padmaja Kandula, Gail E. Solomon, Murray Engel (Child Neurology, New York Presbyterian Hospital – Cornell, New York, NY 10021, USA)

Rationale: Epilepsies of Occipital lobe origin are under recognized as they frequently masquerade as migraine and other seizure syndromes.

Methods: We report two children with atypical presentations of occipital lobe epilepsy.

A 7-year-old boy presented with episodes of dizziness, nausea, vomiting, pallor, blurry vision and unsteady gait occurring 1–2 times/week, lasting 30 min. There was no associated eye deviation or tonic clonic movement. He had been started on oxcarbazepine at an outside hospital with no improvement. EEG showed right occipital diphasic sharp waves. In addition there were bioccipital sharp waves and almost continuous bilateral generalized sharp and slow wave complexes in sleep. MRI was normal. He was started on Depakote with no further events.

A 15-year-old boy came home at night with headache, vomiting and 2 episodes of generalized tonic clonic seizures. Past history was significant for frequent visual hallucinations and headaches for 2 years and a seizure at 7 years of age. His EEG showed left occipital electrographic partial status epilepticus with no significant clinical correlate. The paroxysms did not resolve with eye opening. Electrographic seizures did not respond to IV phenytoin. Oxcarbazepine, IV valproate and IV phenobarbital were used before electrographic seizures resolved. He continues on valproate and oxcarbazepine with no further events. MRI during electrographic status showed diffusion abnormality in left occipital lobe which resolved after seizures were controlled.

Results: The 7-year-old boy’s seizures were atypical in the absence of eye deviation, significant alteration of consciousness and convulsions. Seizures were relatively brief, frequent and did not respond to oxcarbazepine. All were deviations from the usual features of the Panayiotopoulos syndrome.

The 15-year-old boy had some typical clinical manifestations of the Gastaut type of epilepsy with visual hallucinations and headache. EEG monitoring revealed electrographic refractory partial status epilepticus of left occipital origin with no clinical manifestations. The unusual electrographic and MRI findings prompted aggressive management.

Conclusion: Occipital lobe epilepsies often elude diagnosis as they present with inconspicuous manifestations that could be overlooked and with manifestations that are frequently mistaken for more common disorders, especially migraine. The visual phenomenon differ from those associated with migraine and should prompt a more thorough investigation for occipital lobe epilepsies. Atypical presentations like those observed above are another reason for possible misdiagnosis and delayed treatment.

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