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1. Daily DHA injections raise seizure thresholds and blood but not brain free DHA levels in rats—Marc-Olivier Trépanier, Ameer Y. Taha, Richard P. Bazinet, W.M. Burnham (Departments of Nutrition and Pharmacology, University of Toronto, Canada)

Background: Docosahexaenoic acid (DHA) is an omega-3 polyunsaturated fatty acid ($n-3$ PUFA), which has previously shown to have anticonvulsant activity rats. The purpose of the present experiment was: (1) to confirm that sub-chronic DHA raises thresholds in the maximal pentylenetetrazole (PTZ) model, and (2) to determine whether that increase is correlated with an increase in serum and brain DHA

Methods: Animals received daily i.p. injections of 50 mg/kg of DHA, 50 mg/kg DHA ethyl ester (DHA EE) or volume-matched vehicle for 14 days. On day 15, one group of animals was seizure tested in the maximal PTZ model, while another group provided blood and brain samples. Brain samples were obtained after the animals were euthanized via head-focused microwave fixation. Lipid analyses were performed on both blood and brain. Since the DHA and DHA EE groups did not differ significantly, they were combined for statistical analyses.

Results: In the maximal PTZ model, DHA significantly increased seizure latency by approximately 3 fold, as compared to vehicle-injected controls. This increase in seizure latency was associated with an increase in serum unesterified DHA levels. Total brain DHA and brain unesterified DHA, however, were not significantly different between treatment and control groups.

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2. Photoparoxysmal response in patients with migraine and epilepsy—Umang Modi[a,b], Paul Hwang[b,c] ([a]North York General Hospital EEG Lab, Canada, [b]University Of Toronto EEG Research Program, Canada, [c]Ontario Brain Institute-EpLink, Toronto, ON, Canada)

Objectives: 5% of patients with epilepsy and migraines are photosensitive and liable to visually induces seizures. The similarity between intermittent photic stimulation (IPS) that provokes seizures and those provokes minimal discomfort and a headache suggests that the precipitants share a common neural mechanism.

Material and methods: With 10–20 system of electrode placement and Stellate-Harmonie EEG recording system for at least 20 min in bipolar montage with inclusion of ear reference and often sub temporal electrodes. Activation procedures include, eye opening–closing and hyperventilation, for 3–5 min; in early part of recording and IPS near end of recording at a stroboscope distance is 0.5 m from eyes and frequency runs from 1 Hz to 30 Hz every 10 s in incremental fashion.

Results: Photoparoxysmal responses (PPR) are abnormal electrographic response to photic stimulation marked by diffuse paroxysmal discharge occasional minor twitching of fingers or eye balls or clonic movements of the part of body. If it presents with generalized tonic clonic discharge, it is called photoconvulsive response. IPS induces spikes, spike-waves or sometimes intermittent slow waves, bilaterally synchronous, outlasting the end of IPS. It is hypothesized that membrane depolarization of some of the neurons to light stimuli, especially over the posterior head region contribute to photosensitivity.

EEG lab, at NYGH, prevalence of migraine in epileptic population has been assessed at 8.3%, and EEG findings of PPR occurs in 1% of individuals aged 6–18 with seizures where as less than 1% in epileptic patients aged >18. The prevalence figure for migraine is assumed to be 5–10%, where as epilepsy is considered to be 0.5–1%. Prevalence of migraine in epileptic population has been assessed at 8–15%, and prevalence of epilepsy in migrainous population at 1–17%. Lifetime prevalence of 1 in 10,000 in the general population, as low as 2%, of the epilepsy population. PPR is present in 1.3–1.4% of healthy individuals aged 6–18.

Discussion: It's been reported by Ernst and Quesnay that apomorphine, a dopamine receptor agonist, stops clinical and EEG findings of PPR without significantly reduction of spontaneous spike and wave activity. These signify different pathogenic mechanism in origin of spontaneous and evoked generalized epilepsy. It has been shown in cats that decreased endogenous release of dopamine and noradrenaline enhance pre-existing state of cortical excitability. Paroxysmal abnormalities including PPR found increased frequency with migraine and homozygous autosomal recessive inheritance.

PPR sometimes outlasted the stimulus, and self-limited PPR probably have greater significance and are highly correlated with epilepsy. The PPR extending beyond the stimulus carries no increased risk of seizures.Photosensitive epilepsy has a good prognosis for seizure control that is independent of the persistence or disappearance of Photosensitivity. Encephalography has been much dispute in the study of migraine and epilepsy especially when both present as vice-versa triggers. An apparent increase in abnormalities, most of the times nonspecific and used as lateral relationship between migraine and epilepsy in presence of PPR, particularly in children.

Table 1

	Age <18	Age ⩾ 18	PPR in age < 18	PPR in age ⩾ 18
Migraine	20	98	1	0
Seizures(Documented)[a]	100	264	1	2
Seizures + HA	2	8	0	0
N	492			

[a] At least one (past or present) EEG documentation of epileptogenic activity.

Table 1

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3. Severe hypoglycemia in juvenile diabetic rats: Presence and severity of seizures predictive for mortality—Margaret Maheandiran, Shanthini Mylvaganam, Chiping Wu, Youssef El-Hayek, Sonia Sugumar, Rob Vukelich, Martin del Campo, Adria Giacca, Liang Zhang, Peter L. Carlen (Toronto Western Research Institute, University Health Network, Department of Physiology, University of Toronto, Canada)

Background: It is well accepted that insulin-induced severe hypoglycemia is a major limiting factor in the management of diabetes resulting in brain dysfunction and seizures. However, the effects of the seizures and treatment strategies have yet to be elucidated, particularly in juveniles. Here we establish a model of severe hypoglycemia and seizures in juvenile diabetic rats.

Methods: Diabetes was established in post-weaned 22-day-old rats by streptozotocin (STZ; 80 mg/kg) intraperitoneal (IP) injection. After a week, severe hypoglycemia was induced by insulin IP (15 U/kg) in fasted (14–16 h) diabetic (STZ) and non-diabetic (CON) animals. Experiments were video-monitored and seizures scored to quantify behaviour.

Results: Seizures occurred in 86% of STZ and 100% of CON rodents that reached hypoglycemia (defined as <3.5 mM blood glucose). The blood glucose thresholds for seizure onset were not significantly different between these groups; STZ: 1.8 ± 0.2 mM, CON: 1.6 ± 0.1 mM. Mortality in non-seizing animals was 0%, compared to those that seized (STZ: 33%, CON: 42%; $p < 0.05$). Surviving animals exhibited a significantly reduced number of seizures in both CON: survival: 1.6 ± 0.3 ($n = 11$), mortality: 7.8 ± 2.7 ($n = 5$; $p < 0.01$) and survival: S + S: 1.6 ± 0.2 ($n = 17$), mortality: 4.4 ± 1.2 ($n = 5$; $p < 0.001$) groups. Treatment with diazepam, phenytoin and glucose at seizure onset was significantly more successful at ameliorating seizures than glucose alone but did not improve mortality, as subclinical seizures may be present. Intracranial hippocampal and brainstem electroencephalograms (EEG) recorded in nine diabetic hypoglycemic rats showed EEG slowing, but not always EEG suppression, prior to seizures. Electrographic seizure activity was observed in two of the four animals that went on to have seizures.

Conclusions: This model of hypoglycemia and seizures in juvenile diabetic rats provides evidence that severe hypoglycemia (<2.0 mM) is a necessary precondition for seizures, with mortality only occurring in the animals that exhibited seizures.

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4. Familial generalized seizures due to *LGI1* mutation: Importance of family history for genetic testingz—Dina Amrom, Eva Andermann, Frederick Andermann (Montreal Neurological Hospital and Institute and the Departments of Neurology & Neurosurgery, Human Genetics and Pediatrics, McGill University, Montreal, Quebec, Canada)

Background: It is well known that patients with temporal lobe epilepsy may present with generalized seizures, and the temporal localization depends on further investigation.

We present a family with five individuals in three generations where the clinical pattern consisted largely of generalized seizures, but who were then shown to have epilepsy due to an *LGI1* mutation. We wish to discuss the clinical and EEG findings in these patients, and to compare these with families with autosomal dominant partial epilepsy with auditory features (ADPEAF) or familial lateral temporal lobe epilepsy (FLTLE) reported in the literature.

Family report: The proband is a 46-year-old female college graduate who had normal development and no history of head trauma, central nervous system infection or febrile seizures. She had four nocturnal generalized tonic-clonic seizures (GTCS), all occurred around 5–6 am, the first one at age 19 years. Diphenylhydantoin was prescribed and later replaced by carbamazepine CR. She has been seizure free since adequate compliance with treatment. Her first EEG performed at 19 years showed an excess of slow waves at 2–4 Hz over both posterior head regions without epileptic activity. Her second EEG at 22 years showed spikes and slow spike waves alternating over both temporal regions, mostly during drowsiness, and increased during hyperventilation. During intermittent photic stimulation, a photomyoclonic response appeared.

Her 40-year-old sister had her first GTCS at 12 years which was generalized from the onset. All but one of her subsequent attacks occurred during sleep. Before the only seizure that occurred while awake, she felt numbness of her whole body and heard a whooshing sound suggestive of neocortical temporal lobe involvement.

The third sister is 52 years old; she had her first GTCS at 19 years. A year prior to this, she had transient symptoms of a tingling sensation associated with a whooshing noise. She later had other generalized attacks preceded by this aura. A diagnosis of neocortical or lateral temporal lobe epilepsy, possibly ADPEAF or FLTLE, was suggested.

Although the proband only had nocturnal GTCS, ***LGI1*** sequencing was performed on the basis of the family history. A c.611delC mutation leading to a frameshift and premature termination of the protein was identified.

Discussion: Generalized nocturnal and diurnal seizures associated with interictal generalized spike-wave activity occurring in a family with ADPEAF is unusual. They may represent secondarily generalized seizures or primary generalized seizures or both. In addition, photosensitivity in the proband is unusual as well. Among the reported patients with *LGI1* mutation, there are several who have had GTCS and interictal generalized spike-wave and/or polyspike-wave discharges [Ottman et al., 2004].

This family further illustrates that patients with ADPEAF or FLTLE may present with generalized seizures and generalized spike and wave epileptic discharges. Intensive monitoring and attention to aura with auditory features should lead to accurate diagnosis of this genetically determined epileptic syndrome.

This report points to the importance of detailed family history to help orient the diagnosis by genetic testing.

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5. The effects of progesterone, DHP, and THP on spontaneous inter ictal discharges in CA3 electrically kindled mice—Melanie A. Jeffrey, Min Lang, W.M. Burnham, Liang Zhang)

Progesterone is an anticonvulsant neurosteroid. It is reduced by the unidirectional enzyme 5α-reductase to 5α-dihydroprogesterone (DHP) and subsequently reduced by the bidirectional enzyme 3α,5α- hydroxysteroidoxidoreductase to 3α,5α-tetrahydroprogesterone (THP, also called "allopregnanolone"). Progesterone, DHP and THP have protective effects in models of traumatic brain injury, and slows epileptogenesis in kindling models. It is possible that these pregnanes could be anticonvulsant. Since anticonvulsant drugs cannot prevent epileptogenesis, endogenous hormones or their analogues remain attractive potential therapies to improve prognoses after a first seizure.

In CA3-kindled aged male mice, our laboratory found high, sedative doses of progesterone, THP, and the benzodiazepine midazolam to suppress EEG afterdischarges and behavioral seizures. DHP had no anticonvulsant effect. THP and other 3α-reduced neurosteroids are agonists for extrasynaptic GABA-A receptors with δ-subunits, which mediate most tonic inhibition in the brain. Increased tonic, GABAA δ-subunit mediated inhibition decreases IID frequency. Benzodiazepines, by contrast, target GABA-A receptors with γ-subunits, which mediate phasic inhibition in the brain.

Interictal discharges (IIDs) occur spontaneously in kindled animals, and in persons with epilepsy. IIDs represent hyper-excitability of the epileptic brain, and epileptogenesis. Few studies of in vivo IIDs exist, especially outside of psychiatric research. There are no studies of IIDs in electrically kindled animals, or of the effects of pregnane neurosteroids on IIDs.

We are currently investigating the effects of midazolam, progesterone, and its metabolites on IIDs. We hypothesize that progesterone, DHP, and THP may alter epileptogenic processes by reducing tonic hyper-excitability. Midazolam may alter epileptogenic processes by reducing phasic hyper-excitability. Although THP and midazolam were both effective at suppressing behavioral seizures and EEG afterdischarges, we hypothesize that IID differences will exist between progesterone, DHP, THP, and midazolam. These differences may give insight into how midazolam, progesterone, DHP and THP may alter hyper-excitability, and perhaps epileptogenesis, in the kindled mouse brain.

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6. SOTO'S syndrome: A unique cerebral gigantism—Boris Yakubov[a], Espleth Bradley[b], Jeff Kobayashi[b], Paul Hwang[c] ([a]Windsor University, School of Medicine, Ontario Brain Institute, EpLInk, Canada, [b]Hospital for Sick Children and Surrey Place Centre, Ontario Brain Institute, EpLInk, Canada, [c]University of Toronto, Epilepsy Program, Ontario Brain Institute, EpLInk, Canada)

Introduction: Soto's syndrome is a rare genetic disorder caused by a mutation in the NSD1 gene. 95% are sporadic, the rest have Autosomal Dominance pattern of inheritance. In the Japanese population, genetic material is deleted from the region of chromosome 5, containing the NSD1 gene. The NSD1 gene provides instructions for making a protein that is involved in normal growth and development. Excessive physical growth during the first few years of life, macrocrania, mild mental retardation and unusual aggressiveness are the main features of the syndrome. The pathogenesis of this syndrome is not yet fully understood.

Case report: A 41 year old right handed man was referred for behavioural disorder, eyelid flutter and headaches, and question of seizures. Patient was born full-time after prolonged labour, assisted with forceps. He had cardiac failure at 7 weeks of life, due to Wolff–Parkinson–White syndrome, was treated at SickKids. Tonsillectomy and Adenoidectomy was performed at 4 years, and Orchidectomy for testicular carcinoma at 18 years. Operation for Cholesteatoma was performed due to induced right hearing impairment at 36 years. The patient was diagnosed in early childhood with Soto's syndrome with autistic spectrum disorder. Methods used to conclude the diagnoses included MRI studies, with EEG's and Polysomnography. He had global developmental delay with cognitive impairment requiring special education. Patient has mildly dysmorphic features due to macrocrania with anti-mongoloid slant eyes. Diffuse hypotonia with symmetrical deep tendon reflexes, flexor plantars, and apraxic gait are also present. Aggressive behaviour is increasing as he ages.

Results: His MRI showed mild ventricular enlargement and sulcal enlargement with cerebellar tonsils of Arnold Chiari type I. The EEG had a generalised irregular spike wave paroxysm with a suggestion of a frontal prominence at 18 years, and then normalized with maturation. The Polysomnography showed a disordered sleep pattern with spontaneous arousals from slow-wave sleep and periodic limb movements.

Discussion: This case of Soto's syndrome with typical phenotype and neuroimaging is unique for neurophysiologic studies, including several EEGs over four decades showing paroxysmal activity that resolved with cerebral maturation. Global developmental delay with cognitive impairment could be the result of ventricular and sulcal enlargement, and autistic spectrum disorder may be associated with this abnormality. Detailed studies of the mechanisms whereby NSD1 mutation produced the phenotype of cerebral gigantism remain to be analysed. The lack of clarity of how a reduced amount of protein from the NSD1 gene leads to Soto's syndrome is perhaps one of the biggest questions. Maybe with more potential cases and genetic studies performed, we'll be able to figure out the exact pathogenesis of the protein involved.

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7. Convulsive and non-convulsive seizures observed from aging mice following brian ischemia episodes—Liang Zhang (Toronto Western Research Institute, University Health Network, Canada)

Purpose: Stroke is a leading cause of seizures/epilepsy in the aging/aged population, and seizure development after stroke is associated with poorer prognosis. Currently, seizure genesis after stroke

is not well understood, and only limited information is available about post-stroke seizures in aging/aged animals. In particular, early-onset seizures that occur within 24 h post stroke remain to be examined in aging/aged animals. We thus attempted to model the early-onset seizures in aging mice.

Methods: C57 black mice of 16–20 month-old were used. Unilateral hemispheric ischemia was induced by hypoxia-ischemia or middle cerebral artery occlusion (MCAO) models. The animals were under intensive behavioral monitoring and intracranial EEG recordings to detect post-ischemic seizures and then were euthanized for histological assessments of brain injury. Exposure of mouse brain slices to hypoxia-hypoglycemia episodes were used as in vitro model of brain ischemia, and regional population activities were examined via extracellular recordings.

Results: Vigorous convulsive seizures were observed within 24 h following the hypoxia-ischemia or MCAO episode. These seizures were associated with EEG discharges in the brainstem regions but not in the hippocampal and neocortical areas. Development of these convulsive seizures correlated closely with extensive brain injury and poorer overall outcomes. In addition, non-convulsive seizures, characterized by hippocampal and cortical EEG discharges in the absence of convulsions, were observed following the MCAO episode and prior to the convulsive seizures. When examined in brain slices, seizure-like discharges were observed from the hippocampal CA3 area but not from the brainstem or neocortical area.

Conclusions: The early-onset seizures result from severe cerebral ischemia and brain injury. Generation of the convulsive seizures may involve deeper sub-cortical structures particularly the brainstem, and the non-convulsive EEG discharges may originate from the hippocampus. Our data may help understanding genesis of post-stroke seizures in the aging/aged population.

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8. Genetic basis of Mabry's syndrome—Miles D. Thompson, Tony Roscioli, Paul A. Hwang, Peter N. Robinson, Danielle M. Andrade, Peter Krawitz (Department of Pharmacology, University of Toronto, Canada, University of New South Wales, School of Women's and Children's Health, Canada, Pediatric Neurology, North York General Hospital, Division of Neurology, Toronto Western Hospital, Canada, Charité Universitätsmedizin Berlin, Institute of Medical Genetics and Human Genetics, Canada)

We review the discovery of two genes disrupted in Mabry syndrome (hyperphosphatasia with developmental disability; OMIM#239300): a syndrome notable for characteristic facial dysmorphology (hypertelorism, a broad nasal bridge and a tented mouth); subtle hand bone abnormalities (variable shortening of middle and distal phalanges) and nerve abnormalities (plaques disrupting Schwann cells) and persistently elevated serum alkaline phosphatase (ALP). In approximately two thirds of cases, the biochemical abnormalities present in Mabry syndrome result from disruption of the phosphoinositol glycan (GPI) anchor as a result of mutations in the phosphoglycan-inositol biosynthesis type V (*PIGV*) and type O (*PIGO*) genes. The remaining one third of cases have no known mutation in the GPI anchor pathway. These idiopathic cases are reported to accumulate lysosomal storage material that has been putatively identified as a glycolipid material. As twenty genes are integral to GPI anchor synthesis, we hypothesize that idiopathic cases of Mabry syndrome may result from disruptions in other genes encoding GPI anchor biosynthesis enzymes. We are using exome sequencing and candidate gene approaches to identify the gene(s) responsible for idiopathic Mabry syndrome. This work will assist in elucidating the inborn errors of metabolism that underlie the seizures associated with Mabry syndrome.

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