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1. Benign form of Unverricht–Lundborg disease (ULD) mimicking juvenile myoclonic epilepsy (JME) in adulthood—D. Amrom [a,c], M.R. Heshmati Moghaddam [a,c], F. Andermann [b,c,e], A.-E. Lehesjoki [f], E. Andermann [a,c,d] ([a] Neurogenetics Unit, Montreal Neurological Hospital and Institute, Montreal, Quebec, Canada, [b] Seizure Clinic, Montreal Neurological Hospital and Institute, Montreal, Quebec, Canada, [c] Department of Neurology & Neurosurgery, McGill University, Montreal, Quebec, Canada, [d] Department of Human Genetics, McGill University, Montreal, Quebec, Canada, [e] Department of Pediatrics, McGill University, Montreal, Quebec, Canada, [f] Folhalsan Institute of Genetics and Neuroscience Centre, University of Helsinki, Finland)

Rationale: Unverricht–Lundborg disease (ULD) (EPM1) is an autosomal recessive neurodegenerative disease with progressive myoclonus epilepsy (PME). The onset is usually between 6 and 15 years of age with myoclonus and generalized tonic-clonic seizures, variable severity and course, and variable degrees of cognitive deterioration. With good antiepileptic management, the patients can now survive into their 50's and 60's. The gene for this disorder was identified in 1996 as cystatin B (*CSTB*), a cysteine protease inhibitor. The most common mutation is a dodecamer repeat, although rare point mutations have also been described.

Objective: To present an extended phenotype of ULD (EPM1).

Methods: The proband who carried a diagnosis of juvenile myoclonus epilepsy (JME) presented with her partner for preconceptional genetic counseling. Since she had a distant family history of Unverricht–Lundborg disease on the maternal side, carrier screening for the *CSTB* gene was carried out for both, employing detection of the dodecamer repeat expansion and sequencing of the *CSTB* gene to rule out point mutations.

Results: This 30-year-old female had a single generalized tonic-clonic seizure during sleep at the age of 11 years, and onset of myoclonic jerks on awakening at around the same time, which were well-controlled by valproic acid. She carries a clinical diagnosis of JME. She was born prematurely after 25 weeks' gestation weighing 750 grams. Developmental milestones were normal, and she was on the honor roll at school in grade X. She works as a high school teacher for behaviourally challenged children. Both paternal grandparents were of Irish origin; both maternal grandparents were French–Canadian, from the Gaspé peninsula of Quebec. Four siblings of the maternal grandmother were diagnosed clinically with ULD and were known to us; the three affected sisters died in their 20's and 30's, and the affected brother died at age 65. A third degree cousin of the mother had epilepsy and died at 18 years of age. A paternal uncle had a single generalized tonic-clonic seizure at the age of 7 years. A distant cousin of the paternal great grandmother was also said to have PME.

CSTB testing revealed that our patient was a compound heterozygote for two mutations: an expansion of the dodecamer repeat and a splice site c.67–1G > C mutation in intron 1, predicting a deletion of the downstream exon 2 with in-frame deletion of 34 aminoacids (p.delV23_K56). This is the second most common mutation underlying EPM1, and the most common point mutation. The husband has no potential EPM1-causing sequence alterations.

Conclusion: Although ULD is often confused with JME in the early stages of the disease, it is rare to find patients with ULD at age 30 who are as well controlled and high-functioning as this patient. Furthermore, other compound heterozygotes with the same combination of mutations have had more severe phenotypes with progressive deterioration. The reason for the milder phenotype in this individual remains unexplained, and may be due to modifying genes and/or gene–environment interactions.

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2. Amygdala kindled seizures in suspend rats: A reanalysis—McIntyre Burnham, Brian Scott (University of Toronto, Epilepsy Research Program, EpLink, Canada)

Background: There has been a controversy concerning the motor substrate for kindled convulsions. Dr. Daniel McIntyre of Carlton University has argued that kindled motor seizures are driven from the anterior (motor) neocortex in rats, whereas our group at the University of Toronto has argued that they are driven from the brain-stem core. Neocortical convulsions in rats tend to be clonic in nature, whereas brain-stem convulsions can be either clonic or tonic.

Methods: Adult, male, Long–Evans rats were suspended in harnesses that allowed visualization of both fore- and hindlimbs. The development of their motor seizures was videotaped as subjects were kindled from the right basolateral amygdala. The question was whether the developing motor seizures would resemble the convulsions triggered from the neocortex or the convulsions triggered from the brain stem.

Results: All subjects developed motor seizures as a result of daily, low level electrical stimulation of the right amygdala. As previously reported, motor seizures did not develop incrementally, but rather evolved in a stepwise manner - as if separate motor substrates were being recruited. Early in development, motor seizures largely involved face and forelimb clonus, which resembled a cortical pattern. Later in kindling, motor seizures developed tonic elements, including forelimb tonic extensions, which resembled a brain-stem pattern. Of interest, the clonic convulsions seen early in stimulation were accompanied by stiffening of the body and hindlimbs – which

did not resemble a typical tonic hindlimb extension. This stiffening – of unknown substrate – seems to correspond to the rearing seen in Stage 3–5 kindled seizures.

Conclusions: As they develop, kindled convulsions display elements that resemble both cortical and brain-stem convulsive behavior. Future experiments might use pharmacological tools to investigate the drug response of these convulsions. Kindled convulsions, however, also contain an element of body stiffening (rearing?) which is not traditionally associated with either cortical or brain-stem convulsions.

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3. A pilot study of a self-management intervention for cognitive impairment in epilepsy—Tracie A. Caller, Karen Secore, Robert Ferguson, Robert Roth, Jonathan Kleen, Faith Alexandre, Barbara C. Jobst (Dartmouth University, New Hampshire, USA)

Background: Approximately 50% of the 2 million people in the US living with epilepsy will have cognitive problems. Despite the significant impact cognitive functioning has on quality of life, there are limited treatment modalities. Our aim was to assess the feasibility and effectiveness of a self-management intervention to address cognitive dysfunction in adults with epilepsy at Dartmouth–Hitchcock Epilepsy Center.

Methods: HOBSCOTCH (HOme Based Self-management and Cognitive Training CHanges lives) was developed to teach problem-solving strategies and compensatory memory strategies. Adults age 18–65 with epilepsy and subjective cognitive complaints were randomized to receive HOBSCOTCH, HOBSCOTCH+ (which adds working memory training) or care as usual. The primary outcome was quality of life (QOLIE-31), with secondary outcomes of executive functioning, objective memory, and depression as measured by validated scales. In addition, a focus group was conducted to obtain quantitative data about patient satisfaction with the intervention.

Results: as of January 31, 2014, 38 have enrolled, 9 patients have completed the 8-week intervention and 8 controls have returned for 8 week assessments. Three patients enrolled in the intervention groups withdrew from the study. Pilot data ($n = 14$) demonstrated that HOBSCOTCH participants ($n = 5$) demonstrated an improvement in our primary outcome of QOLIE-31 scores as compared to controls (average improvement in score of 9.4 for intervention group vs decrease in score of −6.3 for controls, $p = 0.001$). There was also a significant reduction in depression scores and improvement in executive function and objective memory scores. Qualitative data indicate high satisfaction and subjective improvement in cognitive functioning in day-to-day life.

Conclusions: Cognitive problems are common in epilepsy, are multifactorial, & significantly affect quality of life. This pilot data suggests that a self-management intervention may improve cognitive performance in patients with epilepsy, and may be applicable to other patient populations or clinical settings. The effectiveness of HOBSCOTCH in epilepsy is currently being evaluated in a randomized trial.

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4. Epilepsy in the elderly: Do physicians make the right choices?—L. Royer-Perron, C. Deacon, L-.C. Perrier-Ferland, C. Bocti (University of Sherbrooke, Quebec, Canada)

Objective: To evaluate if published treatment guidelines had an impact on the choice of drug for the treatment of epilepsy in the elderly in the recent years. To examine baseline and follow-up data for the treated patients.

Methods: A retrospective cohort study was conducted at a tertiary care center to identify patients aged 65 and older with new-onset epilepsy. Clinical data and investigation results were collected from baseline to latest available follow-up. The number of patients receiving antiepileptic drugs (AEDs) considered suboptimal (phenytoin, phenobarbital, and primidone) and optimal were compared for the 2001–2005 and 2006–2010 time periods.

Results: A significant reduction in the proportion of patients started on a suboptimal drug was observed between the first and second time period (from 78.1% to 47.3%), mainly explained by a reduction in phenytoin use combined with a rise in levetiracetam use. One year after the index event, there was no difference between the two categories of antiepileptic drugs in terms of recurrence of seizures or change in medication.

Conclusions: Medications received by elderly patients newly diagnosed with epilepsy in this retrospective study were more in phase with recommendations in the latter half of the 2001–2010 decade. Nonetheless, phenytoin remained widely used.

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5. Novel anticonvulsant effects of supraphysiological doses of progesterone in hippocampal-kindled mice—Melanie Jeffrey, Liang Zhang, W.M. Burnham (University of Toronto, Epilepsy Research Program, Canada)

Background: Progesterone is a known anticonvulsant. Progesterone's anticonvulsant effects are generally attributed to its secondary metabolite, 5*a*,3*a*-tetrahydroprogesterone (THP, also known as allopregnanolone), and THP's enhancement of $GABA_A$ receptor activity. Accumulating evidence, however, suggests that progesterone itself may have anticonvulsant effects independent of the $GABA_A$ receptor. Using the enzyme inhibitor finasteride, we explored THP/$GABA_A$-independent anticonvulsive actions of progesterone, in both a mouse model of hippocampal kindling in vivo and in mouse entorhinal slices in vitro.

Methods: Kindled mice were treated with intra-peritoneal injections of progesterone (10, 35, 100 and 160 mg/kg) with or without finasteride pretreatment (50 or 100 mg/kg), THP (1, 3.5, 10 and 30 mg/kg), midazolam (2 mg/kg) and carbamazepine (50 mg/kg). Entorhinal cortical slices were prepared from naïve young mice, and repetitive epileptiform potentials were induced by 4-aminopyridine (100 lM), picrotoxin (100 lM) and finasteride (1 lM).

Results: Progesterone and THP were anticonvulsant, as expected. Pretreatment with finasteride, changed, did not abolish the anticonvulsant effects of progesterone. Progesterone doses of 100 and 160 mg/kg suppressed both hippocampal and cortical afterdischarges. In finasteride-pretreated mice, progesterone at 100 and 160 mg/kg decreased cortical but not hippocampal afterdischarges. With or without finasteride pre-treatment, motor seizure stages were significantly reduced by 100 and 160 mg/kg of progesterone. In brain slices, progesterone at 1 lM inhibited entorhinal epileptiform potentials in the presence of picrotoxin and finasteride.

Conclusions: Supraphysiological doses of progesterone have anticonvulsant effects, via an unknown mechanism, that are independent of both THP and the $GABA_A$ receptor. These results are novel. Further investigation of potential mechanisms is necessary to improve our understanding of neuroendocrinological aspects of seizures and epilepsy.

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6. Ceftriaxone and nonconvulsive status epilepticus (NCSE)—Umang Modi[a,b], Paul Hwang[b,c] ([a]North York General Hospital EEG Lab, Toronto, Ont., Canada, [b]University Of Toronto EEG Research Program, Toronto, Ont., Canada, [c]Ontario Brain Institute-EpLink, Toronto, Ont., Canada)

Purpose: Ceftriaxone related nonconvulsive status epilepticus is least suspected and unusual complication especially patients with renal insufficiency (Pre admission Creatinine 140 microMol/L).

Methods: We reviewed the clinical and electroencephalographic (EEG) characteristics of a patient presented with delirium due to UTI and renal failure in whom developed alteration of consciousness without convulsions associated with continuous epileptiform EEG activity while being treated with ceftriaxone.

Results and conclusion: Patient was given Ceftriaxone as treatment for UTI and treatment for electrolyte imbalance. Patient started having decreased responsiveness and altered level of consciousness. The EEG showed continuous or intermittent bursts of generalized, high-voltage, 1–2 Hz sharp wave activity or sharp and slow wave activity that resembled triphasic waves but completely differentiated from triphasic waves. It was not possible to obtain EEG few days after ceftriaxone discontinuation and level of consciousness improved and patient transferred to nursing home with continue AED (dilantin).

Epoch 1 is EEG after first dose of ceftriaxone and Epoch 2 is 2nd day after discontinuation of ceftriaxone.

It is usually not correlated with the use of ceftriaxone and it is hard to speculate. After evaluating all possible common causes, only thing correlated with this patient was ceftriaxone. Also continued epileptiform activity in presence of dilantin and Lorazepam infusion. The temporal relationship between the start of ceftriaxone therapy and the manifestation of NCSE as well as the withdrawal of ceftriaxone and the improved consciousness within 48 h indicated that ceftriaxone was a causative agent. It has been proposed to be mediated by competitive antagonism of *c*-aminobutyric acid (GABA) in brain, which is the principal inhibitory neurotransmitter in the brain, could lead to a low neuronal threshold for neuronal excitation. Cephalosporins can cause nonconvulsive status epilepticus in setting of poor renal elimination. The clinical picture is difficult to differentiate from that of metabolic encephalopathy unless an EEG is obtained. Physicians should be aware of this potentially dangerous complication.

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7. EEG findings in three patients with Alternating Hemiplegia of childhood (AHC)—Ingrid Park, Paul Hwang (North York General Hospital, UTERP, OBI, EpLink, Canada)

Aim: First reported by Verret and Steele in 1971, Alternating hemiplegia of childhood (AHC) is a rare disorder. The incidence is reported at 1 in 1,000,000 but this is most likely higher as AHC is often misdiagnosed. Infants often present with recurrent attacks of hemiplegia affecting either side of the body, abnormalities of ocular movement, movement disorders, and progressive developmental delay. It has been reported to be associated with mutations in CACNA1A, a calcium channel gene, and ATP1A2, a sodium potassium ATPase gene. It has been reported in large cohort studies that close to 50% of children with AHC will develop epilepsy. The purpose of this study is to examine the EEG finding with patient with AHC to further help clarify diagnosis.

Methods: This paper will explore 3 patients, chart review, with confirmed genetic testing of the APT1A2 gene mutation, EEG findings.

Results: Patient 1(R.G) low background activity in left temporal region, irregular sharp slow ave complex at 2 Hz, mild epileptiform focus in right posterior T6, T4 (temporal region. Patient 2 (A.K). slow wave at 4 Hz over both hemispheres that progressed to vertex waves and hypnagogic hypersynchrony after gamma hydroxbutyrate administration. Patient 3 (A.B), normal EEG.

Summary: Although the findings seen in patient with AHC are not pathognomonic, EEG is still a powerful tool in diagnosing patients especially in situations where genetic testing is not available.

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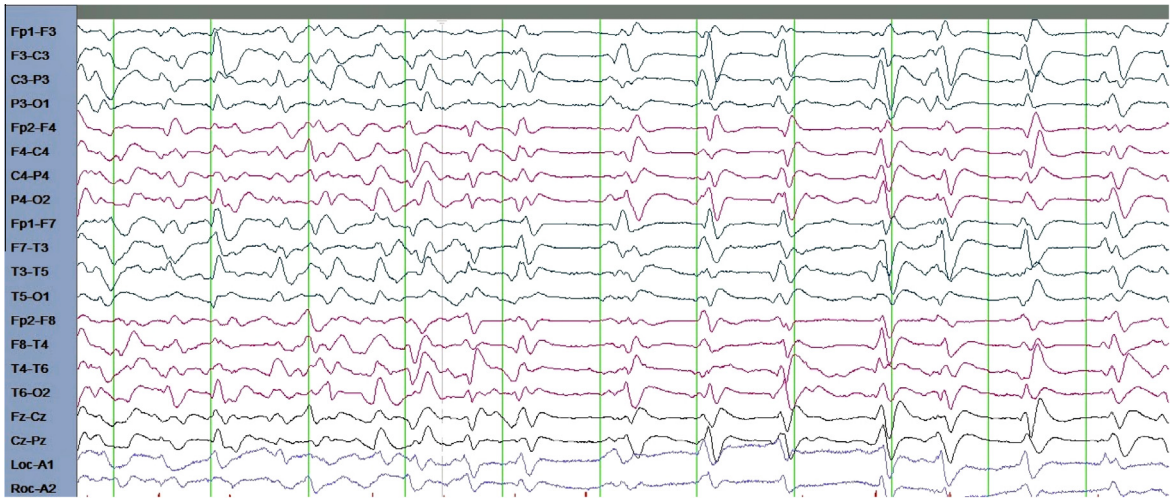
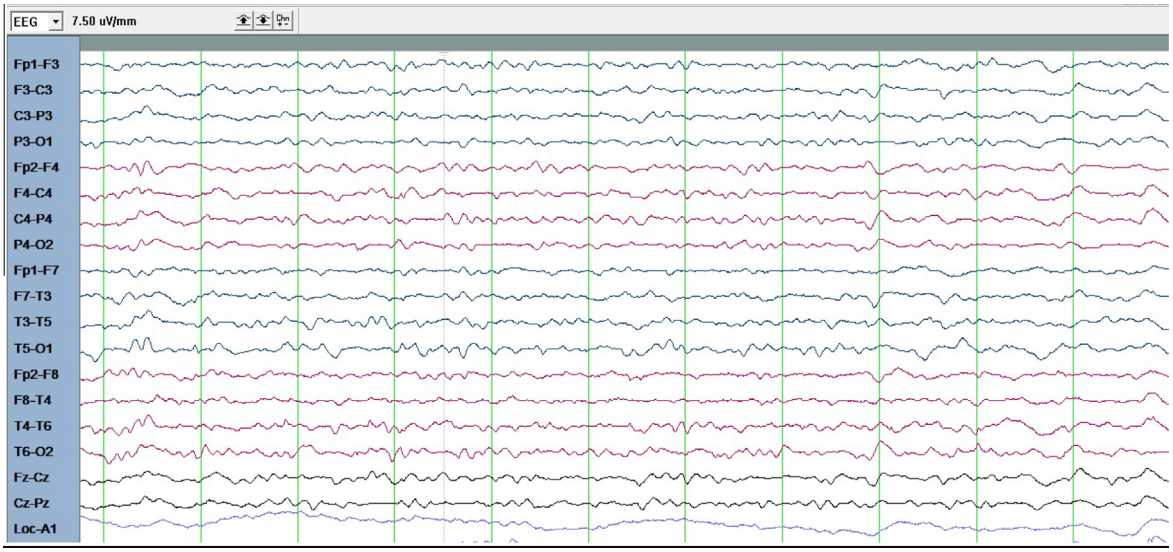
8. Epileptic seizures in adult mice with partial cortical deafferentation—S. Soltani, J. Seigneur, S. Chauvette, I. Timofeev (CRIUSMQ, Québec, Canada)

Traumatic brain injury is a major risk factor for epileptogenesis. Understanding and preventing trauma-induced epileptogenesis (TIE) will prevent epilepsy and therefore significantly increase the quality of life of patients. We aimed to test the age-dependency of TIE in a mouse model of cortical undercut. Because the efficacy of homeostatic plasticity processes decreases with age, we hypothesized that cortical trauma will induce epilepsy in adult, but not young animals. We performed undercut in the somatosensory area in C57/BL6 young (3 months) and adult (12–14 months) mice and



Epoch 1.



Epoch 2.

implanted LFP electrodes in diverse cortical areas and EMG electrodes for chronic recordings. The electrographic activities were recorded continuously for at least two months. Almost all animals generated acute seizures of variable morphology within the first 10 h from lesion.

In young animals only isolated interictal spikes were recorded afterwards. In the following weeks, all but one old mouse revealed recurrent seizure activities of different types. The most common type was 8–16 Hz spindle-like oscillation in frontal cortex accompanied with an increase in the muscle tone and either body freezing or rhythmic contractions. The lower frequency (3–6 Hz) seizures were generalized and accompanied by behavioral freezing and low muscle tone or by rhythmic muscle and body contractions. The low frequency (1.5–3 Hz) seizures were accompanied with rhythmic muscle contractions. We conclude that TIE is age-dependent and is likely due to an uncontrolled homeostatic up-regulation of excitation in adult animals.

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9. Seizures in patients with leptin receptor deficiency: Coincidence or close correlation?—Boris Yakubov [a], Glenn Berall [b], Paul Hwang [c] ([a] Windsor University School of Medicine, Saint Kitts and Nevis, [b] North York General Hospital, Canada, [c] University of Toronto Epilepsy Program, Canada)

Introduction: Leptin receptor also known as LEP-R, is a protein that in humans is encoded by the LEPR gene. LEP-R has also been designated as CD295. Leptin receptors are known to be important in regulating body weight. They are highly expressed in areas of the hypothalamus, as well as in T-lymphocytes, and vascular endothelial cells. Leptin receptor deficiency is a congenital disorder caused by homozygous mutation of LEPR gene, on chromosome 1p31. The mutation could be either missense, nonsense, or frameshift. There is high association with consanguinity. Major symptoms include severe obesity, hyperphagia, and its association with increased susceptibility to Entamoeba Hystolytica infection. Other symptoms include hypogonadism, impulsivity, stubborness, and impaired T-cell mediated immunity. There is also association with seizures. Psychologically patients may show emotional lability and social disability, but no mental retardation.

Case report: A 4 year 10 months old boy was diagnosed with leptin-receptor deficiency at SickKids at age of 1 year. Patient presented with hyperphagia and weight gain. Past history includes febrile seizures between the ages of 1–1.5 years, during teething phase. Shaking spells lasted over 5 min with eyes rolling up and drooling. Patient was born full-time after prolonged labour by C-section. Birth weight was 7 lb, and 6 oz. Patient had increased appetite, which led to referral to SickKids Genetic Metabolic Service. Parents had to lock up the refrigerator and cupboards of food to avoid food stealing. Patient is on RYG diet, as well as on Topiramate and Sertraline. The patient had normal developmental milestones. Weight at 4 year 10 month of age was 30.5 kg. Height of 107.5 cm, with head circumference of 50.6 cm. A 22-channel EEG with polygraphic recording of EMG, EOG, and EKG was performed in regards to febrile seizures.

Results: Patients EEG was moderately abnormal. There was an active epileptiform focus in the left frontocentral region, on two occasions triggering right partial motor seizure activity.

Discussion: This case of leptin receptor deficiency is unique for neurophysiologic studies, including EEG studies performed. Leptin reduces excitability in some hypothalamic neurons via leptin receptor activation of the JAK2 and PI3K intracellular signaling pathways. Whereas mutation of LEPR gene results in abnormal splicing of leptin-receptor transcripts, and generates a mutant leptin receptor that lacks both transmembrane and intracellular domains. In this patient, there is a high probability that a lack of JAK2 and PI3K activation caused neuronal excitation in the hypothalamus, which activated seizure activity. Hypothalamus has high association with gelastic seizures, but more studies need to be done to determine the exact correlation between leptin receptor deficiency and seizure activity. Perhaps with more potential cases and continued research, we will eventually better understand the connection between leptin receptors and its hormones in the hypothalamus.

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