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1. Autonomic changes following traumatic brain injury (tbi)—M.G. Sumner, P.A. Hwang (University of Toronto Epilepsy Research Program, Division of Neurology, Department of Pediatrics, North York General and Toronto Western Hospitals, Toronto, Ont., Canada)

Objective: To explore autonomic changes associated with TBI.

Rationale: Autonomic changes are associated with TBI, either as a direct result of severe TBI, a consequence of seizures, or of severe pain.

Method: Three cases of dysautonomia associated with TBI, with literature review.

Results: In severe TBI autonomic changes may be a direct consequence of the injury, or may cause epilepsy in severe cases. In less severe cases epilepsy can develop as a sequela of TBI-induced epileptogenesis The regions of the brain most likely to be damaged are the inferior portions of the frontal and temporal lobes and diffuse subcortical white matter in the hemispheres and the brainstem. These injuries can produce neuropsychiatric problems and neural reorganization or may trigger seizures. The seizures themselves can produce autonomic and mood changes. The treatment of choice are the mood stabilizers and the anticonvulsants. The fact that seizures and mood changes are both responsive to some of the anticonvulsants implies there is at least some commonality between these conditions.

Chronic pain is very common after TBI, and may be considered a neurodegenerative disorder which may further trigger seizures, but the exact mechanism is unknown. Autonomic dysfunction is common with chronic pain.

Conclusion: Autonomic changes are common after TBI and these changes are related to seizure-like phenomena. Chronic pain is common after TBI. It is speculated that chronic pain produces seizures which produce further autonomic changes, but this process needs to be investigated further. The validity of this proposed hypothesis requires further elucidation.

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2. Cyst-like tubers are associated with TSC2 and epilepsy in tuberous sclerosis complex—Catherine J. Chu-Shore [1], Philippe Major [2], Maria Montenegro [1], Elizabeth Thiele [1] ([1] Department of Neurology, Massachusetts General Hospital, Boston, MA, USA, [2] Service de neurologie, CHU Sainte-Justine, Montreal, QC, Canada)

Background: Tuberous sclerosis complex (TSC) is a genetic condition characterized by the presence of hamartomatous lesions in multiple organs, including tubers in the brain. The majority of patients with TSC have epilepsy. Some cortical tubers are epileptic foci, while others appear to be physiologically quiescent. It is unknown whether or not variations in tuber morphology may account for this difference. The objectives of this study were to (1) determine the frequency of cyst-like tubers in patients with TSC (2) determine whether cyst-like tubers correlate with TSC genotype and (3) determine whether cyst-like cortical tubers are associated with a history of infantile spasms, epilepsy, or refractory epilepsy.

Methods: A retrospective chart review was performed of 173 patients with TSC. MRI images were evaluated for the presence of at least one cyst-like cortical tuber. Patient charts were then reviewed for genetic mutation, a history of infantile spasms, epilepsy, and epilepsy refractory to more than three medications.

Results: 46% of patients had at least one cyst-like cortical tuber present on neuroimaging. Patients with a TSC2 mutation were more likely to have a cyst-like tuber than patients with TSC1 mutation ($p = 0.002$) or patients with no mutation identified (NMI, $p = 0.039$). Patients with at least one cyst-like cortical tuber were more likely to have a history of infantile spasms ($p = 0.00005$), epilepsy ($p = 0.0038$) and refractory epilepsy ($p = 0.0007$) than patients without a cyst-like cortical tuber.

Conclusion: Cyst-like cortical tubers are strongly associated with the TSC2 gene mutation and a more aggressive seizure phenotype in patients with TSC.

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3. Titration to monotherapy: A new paradigm for AED clinical trials—Paul A. Hwang [1], Mac Burnham [2] ([1] Depts. of Paediatrics and Medicine, North York General & Toronto Western Hospitals, [2] Dept. of Pharmacology, University of Toronto Epilepsy Research Program, Ont., Canada)

Objective: Based on a white paper submitted by J. French et al. to the FDA for new antiepilepsy drug (AED) randomized clinical trials (RCTs), it is proposed that placebo-controlled parallel-group RCTs are no longer the 'gold standard' for testing of new AEDs for release in N. America.

Methods: With the numerous RCTs over 30 years, almost all with placebo controls, the cumulative experience with placebo responses

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in epilepsy is well documented and forms an historical control database, at least for refractory complex partial seizures of temporal lobe origin, the most prevalent form of localization-related epilepsy in adults.

Results: The addition of a novel AED in the regimen of 2 or more AEDs for partial seizures in a dose-dependent RCT may allow for the dose titration of the AEDs over a period of several months, tapering off the original AEDs, leading to efficacy studies of the new AED in monotherapy in a dose-dependent response with efficacy outcome. The application of this novel RCT to AED studies using a new AED is illustrated. Potential adverse effects and benefits are critically analyzed and discussed.

Conclusion: The method of titration to monotherapy may constitute a new paradigm in RCTs of new AEDs prior to clinical release, with potential benefits of cost-saving, minimalization of adverse effects and drug interactions and possibly to timely release of new AEDs for monotherapy rather than adjuctive polytherapy of partial epilepsy.

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4. Epileptic negative myoclonus in atypical benign partial epilepsy: Case reports and review of pathophysiology and treatment—Shefali Karkare, Sabiha Merchant, Jacqueline LaMothe, Gail Solomon (NY Presbyterian Hospital/Weill Cornell Medical College, New York, NY, USA)

Epileptic negative myoclonus (ENM) is a heterogeneous clinical condition characterized by brief lapses (usually <500 ms) of tonic muscular contraction at times attributable to anatomical lesions at various levels in the central nervous system.

The association with atypical benign partial epilepsy (ABPE) of childhood although reported is relatively uncommon.

Two children with atypical benign partial epilepsy who later developed ENM manifesting as postural lapses of muscle tone are described here. Interictal EEG of both patients during wakefulness showed independent centroparietal and centrotemporal discharges that were activated during sleep consistent with ABPE.

During lapses of postural tone generalized bursts of moderate to high amplitude 3–4 Hz spike and wave discharges were noted to occur.

Our first patient reported onset of ENM soon after initiation of levetiracetam and worsening on increasing doses of the same. Second patient did not respond to levetiracetam at high dose. Aggravation of ENM has not previously been reported on levetiracetam. Both patients responded well to drugs known to improve ENM, such as valproic acid and clonazepam. Our second case had a well-defined lesion involving right frontoparietal cortex. Frontoparietal cortical generators have been described in literature based on dipole analysis.

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5. A new dietary approach to seizure control—McIntyre Burnham, Ameer Taha (Dept. of Pharmacology, University of Toronto, Toronto, USA)

For many years, there has been interest in the question of whether a special diet of some sort could be used to help in the control epileptic seizures. The ketogenic diet has been used since the 1920s, but it is used only in children, and is so nutritionally unbalanced that it is typically withdrawn after two–three years.

Our recent research now suggests that there may be a new, healthy, long-term dietary approach to controlling seizures. This would take the form of a diet enriched in the omega-3 polyunsaturated fatty acids (*n*-3 PUFA's). We have now been able to show that the *n*-3 PUFA's elevate seizure threshold in several different experiments.

Our initial work was an attempt to replicate the studies of Yehuda's group (Yehuda et al., 1994; Rabinovitz et al., 2004). These studies claimed to show *n*-3 PUFA anticonvulsant effects in animal seizure models. Our replication involved 21 days of the intraperitoneal (i.p.) administration of 40 mg/kg of the SR-3 mixture (linoleic and *a*-linolenic in a 4 to 1 ratio) to Wistar rats, followed by testing in the maximal pentylenetetrazol (PTZ) model. We were not able to show any significant effect of the SR3 mixture at a dose of 40 mg/kg.

We realized, however, that 40 mg/kg represents just a small fraction of a rat's daily dietary intake of the *n*-3 PUFA's (<1.2%). We therefore tested the effects of 200 mg/kg of the SR-3 mixture, administered i.p. for 21 days. At 200 mg/kg, we found a significant increase in the latency to onset of maximal PTZ seizures – although there was no change in seizure severity.

Next, in rats with implanted electrodes, we found elevated seizure thresholds in both the cortex and the amygdala of rats fed a diet enriched with *n*-3 PUFA's (marine fish oils). The elevation in the amygdaloid threshold required a higher dose of *n*-3 PUFA's – a finding consistent with our early finding that higher doses of anticonvulsants are required to suppress amygdala focal seizures in the kindling model (Albright and Burnham, 1980).

Finally in dose-response studies in the maximal PTZ model, we have found that acute s.c. injections of decosohexaenoic acid (DHA), an *n*-3 PUFA, increase latency to seizure onset, while EPA, DHA's precursor does not.

Thus, it is possible that these cheap, easily available, and safe compounds might be added to the anticonvulsant drugs in the treatment of epilepsy.

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6. Assessing the link between omega-3 fatty acids, cardiac arrest, and sudden unexpected death in epilepsy—Flaviu Ciobanu, Ameer Taha, Anjali Saxena, McIntyre Burnham (Dept. of Pharmacology, University of Toronto, Toronto, USA)

People with epilepsy may also have abnormal cardiac function. This has been linked to a greater incidence of sudden unexpected death in epilepsy (SUDEP). In the present discussion, we assess the evidence linking cardiac failure to SUDEP, and propose the use of the maximal pentylenetetrazol seizure test to model SUDEP in animals. We also discuss the possibility that the dietary administration of omega-3 polyunsaturated fatty acids (*n*-3 PUFA's) might not only raise seizure thresholds, but that it might also reduce the incidence of SUDEP because of the *n*-3 PUFA's documented cardioprotective effects.

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7. Homozygosity mapping in Mabry syndrome: A syndrome with hyperphosphatasia with seizures, neurologic deficit and characteristic facial features—Miles D. Thompson [1], Marjan M. Nezarati [2,3], Charleton C. Mabry [4], Matthew A. Deardorff [5], Gabriele Gillessen-Kaesbach [6], Peter Meinecke [7], Catherine Prost Squarcioni [8], Laurence Legeai-Mallet [9], Arnold Munnich [9], Kathy Simi-

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Persistent hyperphosphatasia associated with developmental delay and seizures was first described by one of us (Mabry et al.) in 1970 a single family (OMIM#239300) [1970], but the nosology of this condition has remained uncertain. Our international consortium has identified at least ten cases of Mabry syndrome, in addition to the three cases reported in 1970. Common to all cases is a facial dysmorphism, with hypertelorism, a broad nasal bridge and a tented mouth. All cases have some degree of brachytelephalangy, but the phalangeal shortening varies in position and degree. In all, there is a persistent elevation of alkaline phosphatase activity without any evidence for active bone or liver disease. The degree of hyperphosphatasia varies considerably (~1.3 to 20 times the upper age-adjusted reference limit) between cases, but is relatively constant over time. Although not common to all patients meeting the criteria for Mabry syndrome, the original cases reported in 1970 and two further cases identified in France were found to have intracellular inclusions on biopsy of some but not all tissues. Attempts to identify the intracellular storage material are underway. Since evidence of sibling recurrence and consanguinity suggest that the condition is putatively inherited in an autosomal recessive pattern, we have conducted a whole genome linkage scan in order to identify homozygosity. A 28-Mb region on chromosome 1p was identified – a region that includes the alkaline phosphatase gene. Several other regions of homozygocity have been identified in some patients, suggesting that the syndrome may be heterogenious. Our objective is to identify endophenotypes that are associated with specific genetic variants, thereby allowing the description of genetic basis for the spectrum of syndromes that are currently considered putative cases of Mabry syndrome.

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