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ENCEPHALOPATHIES

ACUTE ENCEPHALOPATHY WITH DRAVET SYNDROME

Researchers at thirteen university medical schools in Japan report 15 patients with Dravet syndrome complicated by acute encephalopathy. Cases were collected through the mailing list of the Annual Zao Conference on Pediatric Neurology. Seven were boys and eight girls. Nine showed a mutation of the *SCN1A* gene (truncation in 6 and missense in 3). The onset of encephalopathy at a median age of 44 months (range 8-184 months) was preceded by status epilepticus and coma as the initial manifestation. Seven children had seizures monthly during 3 months before the onset of acute encephalopathy. MRI during the acute phase showed cerebral cortex-dominant lesions with or without deep gray matter involvement or subcortical-dominant lesions. Four children died; 9 survived with severe sequelae, and 2 had moderate sequelae. (Okumura A, Uematsu M, Imataka G, et al. Acute encephalopathy in children with Dravet syndrome. **Epilepsia** January 2012;53:79-86). (Respond: Akishisa Okumura, MD, Department of Pediatrics, Juntendo University, School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. E-mail: okumura@juntendo.ac.jp).

COMMENT. Acute encephalopathy complicating Dravet syndrome in children and presenting with status epilepticus has a poor prognosis. The authors define acute encephalopathy as a decreased consciousness lasting >24 hours in association with symptoms of infection. *SCN1A* gene mutations were present in 60% of their childhood series, a similar prevalence to that reported in a series of 22 adult cases (Catarino CB et al. **Brain** 2011;134:2982-3010; **Ped Neur Briefs** Nov 2011;25:85). In a series of 16 Dravet syndrome patients followed at Children's Memorial Hospital, Chicago, 6 of 7 patients (86%) tested positive for *SCN1A* mutations. (Korff C, Laux L, Kelley K, Goldstein J, Koh S, Nordli D Jr. **J Child Neurol** 2007;22(2):185-194).

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A review of the genetics of Dravet syndrome (severe myoclonic epilepsy of infancy, SMEI) finds a genetic etiology and *SCN1A* mutations in 70% - 80% of patients; in 20% the cause is unknown. Are *SCN1A* gene abnormalities essential for the diagnosis of Dravet syndrome, or are other genes sometimes involved? (Marini C et al. **Epilepsia** 2011;52 (Suppl 2):24-29). Five alleged cases of pertussis vaccine encephalopathy were rediagnosed years later as Dravet syndrome, testing positive for *SCN1A* mutations. (Reyes IS et al. **Pediatrics** 2011;128(3):e699-e702). More frequent *SCN1A* genetic testing in infants with refractory myoclonic seizures should lead to earlier diagnosis and more effective treatment of Dravet syndrome cases.

COPY NUMBER VARIANTS IN EPILEPTIC ENCEPHALOPATHY

An international group of investigators at University of Washington, Seattle, USA, and various centers in Australia, New Zealand, Canada, and Israel evaluated 315 patients with epileptic encephalopathies for rare copy number variants (CNVs) using a whole-genome oligonucleotide array. Twenty five (7.9%) patients carried rare CNVs thought to contribute to their phenotype, one half being pathogenic. Several novel candidate genes for epilepsy were uncovered. Array comparative genomic hybridization (CGH) should be considered in the genetic evaluation of patients with epileptic encephalopathy characterized by severe epilepsy and cognitive regression. (Mefford HC, Yendle SC, Hsu C, et al. Rare copy number variants are an important cause of epileptic encephalopathies. **Ann Neurol** Dec 2011;70:974-985). (Respond: Dr Heather C Mefford, 1959 NE Pacific St, Box 356320, Seattle, WA. E-mail: hmefford@u.washington.edu).

COMMENT. Epileptic encephalopathies (EEs) are severe epilepsies in which the epilepsy activity contributes to cognitive impairment or regression and poor outcome. Most EEs begin in infancy or childhood, often associated with normal development initially and with subsequent cognitive decline. These cases differ from those epilepsies with static intellectual disability. Copy number variants are an important source of gene mutation in neurocognitive disorders and the epilepsies.

The gene content of copy number variants found in 11 subjects with infantile spasms was involved in abnormalities of ventral forebrain development and pathways of synaptic function (Paciorkowski AR et al. **Eur J Hum Genet** 2011;19(12):1238-1245).

EPILEPTIC ENCEPHALOPATHIES, CDKL5 MUTATIONS, AND INFANTILE SPASMS

Researchers at the Mayo Clinic, Rochester, MN performed retrospective chart reviews of 6 children with epilepsy and CDKL5 mutations. Four were girls and 2 boys. All developed infantile spasms after the majority (4/6, 67%) presented with partial-onset seizures. Five had dysphagia, profound in 4. The EEG revealed hypsarrhythmia in 3 children and modified hypsarrhythmia in 2. Mean age of seizure onset was 1.8 months (range, 1-3 months). Four had hypotonia, and all had developmental delay and cortical visual impairment. Topiramate, vigabatrin, and the ketogenic diet were of most benefit, but all had refractory seizures at follow-up. Steroids or ACTH were used in 4 patients, without complete seizure control. Boys and girls were affected equally, despite the X-

linked mutation involved. Screening for CDKL5 mutations is recommended in children with epileptic encephalopathies of unknown origin and infantile spasms. (Moseley BD, Dhamija R, Wirrell EC, Nickel KC. **Pediatr Neurol** February 2012;46:101-105), (Response: Dr Moseley, Department of Neurology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905. E-mail: moseley.brian@mayo.edu).

COMMENT. The authors list several genetic defects that predispose children to early-onset epileptic encephalopathies and infantile spasms, previously considered cryptogenic. The *CDKL5* mutations are thought to influence brain development via a similar molecular pathway to *MECP2*, the mutation that causes the majority of Rett syndrome cases. However, none of the authors' *CDKL5* cases demonstrate the typical Rett syndrome-like phenotype with hand stereotypies, and only 1 has a characteristic microcephaly. Seizures with *CDKL5* mutations are refractory to treatment including the ketogenic diet, whereas the majority (56%) of children with Rett syndrome and *MECP2* mutations have treatment-responsive seizures. (Krajnc N et al. **J Child Neurol** 2011;26:1429-1433). The authors' suggestion that acidosis is a possible mechanism of the ketogenic diet is contrary to earlier research conducted at the Mayo Clinic (Millichap JG et al. **Amer J Dis Child** 1962;107:593-604, and *idem* **Epilepsia** 1964;5:239-255).

***KCNQ2* Encephalopathy, an emerging phenotype of a neonatal epileptic encephalopathy** is reported in 8 patients with early onset intractable seizures (first week of life) with prominent tonic component. (Weckhuysen S, Mandelstam S, Suls A, et al. **Ann Neurol** January 2012;71:15-25). Seizures resolved by 3 years but residual intellectual disability and motor impairment were severe. EEG at onset showed a burst-suppression pattern or multifocal epileptiform activity. Early brain MRI showed hyperintensities in basal ganglia and thalamus that later resolved. KCNQ2 screening should be considered in the workup of refractory neonatal seizures of unknown origin.

HASHIMOTO ENCEPHALOPATHY AND STATUS EPILEPTICUS

A 12-year-old boy with Hashimoto encephalopathy and drug-resistant status epilepticus responsive to plasmapheresis is reported from Ankara University Medical School, Turkey. He was admitted with a right focal seizure, becoming secondary generalized tonic-clonic, refractory to treatment and necessitating a pentobarbital-induced coma. Recent history revealed a sudden change in personality, fever, headache, and fatigue, indicating limbic encephalitis. Serum anti-thyroid peroxidase antibody was elevated at 30 IU/ml (normal range, 0-9 IU/ml). Treatment with iv immunoglobulin was ineffective, and plasmapheresis was performed, followed by levothyroxine and oral prednisolone (2 mg/kg/day). The neurologic and psychiatric manifestations (orofacial dyskinesia, autonomic instability, emotional lability, and personality changes) decreased after the eighth plasmapheresis, and his examination was normal after 2 months. He was discharged taking prednisolone (1 mg/kg/day), levothyroxine, and antiepileptic drugs. (Bektas O, Yilmaz A, Kendirli T, Siklar Z, Deda G. Hashimoto encephalopathy causing drug-resistant status epilepticus treated with plasmapheresis. **Pediatr Neurol** February 2012;46:132-135).(Respond: Dr Bektas, Department of Pediatric Neurology, Ankara University Medical School, Ankara, Turkey. E-mail: bektasomer@gmail.com).

COMMENT. Hashimoto encephalopathy (HE) is characterized by seizures, neurologic and psychiatric manifestations, and elevated titers of serum anti-thyroid antibodies. It is responsive to corticosteroids. Plasmapheresis is a novel method of acute treatment. HE should be considered, along with anti-N-methyl-D-aspartate-receptor, voltage-gated potassium channel antibody-associated limbic encephalitis, and herpes simplex virus encephalitis, in the differential diagnosis of a child with acute personality changes and seizures resistant to antiepileptic medication. The pathogenesis of HE is associated with high serum anti-thyroid antibody titers; thyroid hormone levels are usually normal or slightly low. An autoimmune disease process is likely.

POLG NOVEL MUTATION WITH ALPERS SYNDROME

Researchers at University Hospital, Berne, Switzerland describe the molecular genetic analysis of *POLG* in a 3.5 years old boy with VPA-induced fatal liver failure and encephalopathy (Alpers-Huttenlocher syndrome, AHS). Mutations in the *POLG* gene are a common cause of inherited mitochondrial disease in children and adults. They are involved with various neurodegenerative diseases, including Alpers syndrome, and result in accumulation of multiple mtDNA deletions and/or depletions of mtDNA in muscle, brain and liver. Some *POLG* mutations lead to a range of clinical phenotypes that predispose to fatal liver failure after exposure to VPA. *POLG* analysis in mitochondrial diseases helps in confirmation of AHS and optimizes clinical management. (Schaller A, Hahn D, Jackson CB, et al. Molecular and biochemical characterization of a novel mutation in *POLG* associated with Alpers syndrome. **BMC Neurology** 2011;11:4-11). (Respond: Dr Andre Schaller. E-mail: andre.schaller@insel.ch).

COMMENT. The study extends the list of *POLG* mutations associated with VPA hepatoxicity. A report of reversible valproate hepatotoxicity due to mutations in mitochondrial DNA polymerase gamma *(POLG1*) is cited. (McFarland R et al. **Arch Dis Child** 2008;93(2):151-153).

DEMYELINATING DISEASE

HEAD AND BRAIN SIZE IN PEDIATRIC MULTIPLE SCLEROSIS

Researchers at the Montreal Neurological Institute, the Hospital for Sick Children, Toronto, Canada; and Department of Neurology, Rennes, France conducted MRI measurements of whole brain and regional white matter, gray matter, and deep gray matter structure volumes in 38 patients (mean age 15.2+/-2.4 years) with pediatric-onset relapsing-remitting multiple sclerosis (MS). Mean age at MS onset was 12.1 years; mean disease duration 3.1 years. Values obtained from sex-matched healthy controls enrolled in the MRI Study of Normal Brain Development were used as controls. The intracranial volume and normalized brain volume z scores were significantly lower in patients with MS compared with controls. Thalamic volumes in MS patients were lower even after correction for global brain volume decreases. Reduced thalamic and brain volumes

correlate moderately with increased disease duration. Head size of pediatric MS patients is lower than controls. (Kerbrat A, Aubert-Broche B, Fonov V, et al. Reduced head and brain size for age and disproportionately smaller thalami in child-onset MS. **Neurology** January 17, 2012;78(3);194-201). (Response and Reprints: Dr Collins, E-mail: louis.collins@mcgill.ca).

COMMENT. Onset of MS during childhood is associated with smaller head size, brain volume, and even smaller thalamic volume. Cognitive impairment is a notable feature of pediatric MS. (Amato M et al. **Neurology** 2007;70:1891-1897), and thalamic volume correlates with cognitive performance of children with MS. (Till C et al. **Neuropsychology** 2011;25;319-332).

HEADACHE DISORDERS

SHARED GENETIC ETIOLOGY FOR MIGRAINE AND EPILEPSY

Shared loci for migraine and epilepsy were found on chromosomes 14q12-q23 and 12q24.2-q24.3 in a linkage analysis study of a Finish family with a complex phenotype, in a report from Folkhalsan Institute and other centers in Helsinki and Oulu, Finland; University of California, Los Angeles; and Wellcome Trust Sanger Institute, Cambridge, UK. Of 60 family members, 12 (20%) had idiopathic epileptic seizures, and 8 of the 12 (67%) also had migraine. Seven (12%) had febrile seizures. (The novel migraine locus identified on chromosome 12 has previously been linked to febrile seizures [Gurnett CA et al. **Neurogenetics** 2007;8:61-63]). Ten family members (17%) had sudden somnolence lasting a few minutes to 2 hours and associated with centrotemporal EEG abnormalities. Thirty-three of the 60 family members (55%) had migraine (20 [33%] without and 13[22%] with aura), and 37 (62%) had either migraine or epilepsy. Nine (15%) family members had both migraine and epilepsy. (Polvi A, Siren A, Kallela M, et al. Shared loci for migraine and epilepsy on chromosome 14q12-q23 and 12q24.2-q24.3. **Neurology** January 17, 2012;78:202-209). (Response and Reprints: Dr Polvi. E-mail: anne.polvi@helsinki.fi).

COMMENT. Migraine and epilepsy share a common genetic etiology. Of patients with migraine, 6% have epilepsy and up to 26% of patients with epilepsy have migraine (Ottman R, Lipton RB. **Neurology** 1994;44:2105-2110 and others, cited by authors). Antiepileptic medications are effective in the prophylaxis of migraine. (Barbanti P et al. Migraine prophylaxis: what is new and what we need? **Neurol Sci** 2011;32(suppl 1):S111-S115).

EFFECT OF HEADACHE ON ACADEMIC PERFORMANCE

Researchers at University of Pernambuco, Recife, Brazil interviewed 344 randomly selected, university, social communication students to determine the 1-year prevalence of headache, types of headache, and the effects on academic performance. The mean age was 23.4 years; 57.3% were women. Headache prevalence was 87.2%

(migraine 48.5%, tension-type 42.4%). In the 3 months before the interview, 8.7% sought emergency services because of headaches, 30.8% missed classes, 30.8% were less productive, 75.6% used analgesics, 1.5% reported analgesic overuse, and headache had a substantial/severe impact on daily activities in 49%. Multiple linear regressions showed that serious-impact headaches are significantly related to a greater number of subject failures and absenteeism, and are associated with worse academic performance. Neither anxiety (in 43.9% students) nor depression (in 18.9%) had a significant effect on grade point average. No headache variables were associated with the grade point average coefficient, whereas individuals who consumed alcohol (52.3%) had a smaller grade point average. (Souza-e-Silva HR, Roche-Filho PAS. Headaches and academic performance in university students: a cross-sectional study. **Headache** Nov-Dec 2011;51:1493-1502). (Respond: Dr Pedro AS Rocha-Filho, E-mail: pasrf@ig.com.br).

COMMENT. Headaches in 50% of university students are severe and may be associated with poorer academic performance. Migraine prophylaxis and reduction of impact of headache severity on social and cognitive functioning might be expected to benefit academic performance. However, data from controlled studies of drugs frequently prescribed for migraine prophylaxis (amitryptiline, valproate, topiramate, and levetiracetam) are insufficient for appraisal. (Lewis D, et al. AAN Practice Parameter: pharmacological treatment of pediatric migraine headaches. **Neurology** 2004;63:2215-2224). Headache is not correlated with grade point average, whereas alcohol consumption has a significant association with a lower grade point average, and the risk of failure increases with the quantity of alcohol consumed. (Lopez-Frias M et al. **J Stud Alcohol** 2001;62:741-744, cited by authors).

COGNITIVE DISORDERS

ROLE OF THE CEREBELLUM IN COGNITIVE FUNCTION

Researchers in the Department of Psychology, University of Rome, Italy, retrospectively analyzed charts from patients in the Ataxia Lab of Santa Lucia Foundation between 1997 and 2007, focusing on the role of the cerebellum in cognition. Of 223 charts of cerebellar patients, mostly adults, 67 were excluded because the pathology was not restricted to the cerebellum; 156 comprising 84 males and 72 females were selected for analysis. Patients with focal or atrophic damage were grouped by etiology or location of the lesion. Focal lesions were ischemic or hemorrhagic stroke or surgical ablation for AV malformation or tumor. MRI was used to identify the lobular distribution of the lesion. Twelve different cerebellar atrophic lesions were represented by 16 cases of olivo-ponto-cerebellar atrophy, 15 idiopathic, 11 Friedreich's ataxia and the remainder as 1-5 cases each. In the clinical focal subgroup of 118 cases, 64 involved cerebellar deep nuclei, 25 the distribution of the posterior inferior cerebellar artery, and 12 the superior cerebellar artery.

Subjects with cerebellar damage had below average z-scores for all cognitive domains. Language, executive function, visuospatial abilities and sequencing are most severely affected functions. Subjects with lesions in the posterior inferior cerebellar artery territory exhibit the worst cognitive patterns, especially affecting sequencing,

similar to those with lesions of the deep cerebellar nuclei. Vascular topography and involvement of deep cerebellar nuclei are the chief factors that determine the cerebellar cognitive profile. The findings support a model in which sequencing is the basic function of the cerebellum. (Tedesco AM, Chirocozzi FR, Clausi S, Lupo M, Molinari M. The cerebellar cognitive profile. **Brain** Dec 2011;134;3669-3683). (Respond: Marco Molinari MD PhD, Neurorehabilitation Santa Lucia Foundation, Via Ardeatina, 306 00179 Roma, Italy. E-mail: m.molinari@hsantalucia.it).

COMMENT. The cerebellar cognitive affective syndrome includes impairments in executive functions, spatial cognition, language and personality changes in patients with cerebellar pathologies. In addition to executive function impairments, visuospatial functions, working memory, verbal memory, linguistic processing, verbal fluency, attention, sequencing and emotion are involved. This study including a large number of patients with cerebellar pathology provides a more comprehensive description of the variety and localization of cerebellar lesions and the specific type of cognition affected, especially sequencing. Subjects with lesions in the posterior inferior cerebellar artery territory and lesions in the deep cerebellar nuclei of the posterior lobe (dentate, emboliform, fastigial, globose nuclei) exhibit the worst cognitive patterns. Cerebellar lesions do not eliminate cognitive function, but they impair motor and mental task performance, causing a "dysmetria of thought." (Schmahmann JD and Sherman JC. The cerebellar cognitive affective syndrome. **Brain** 1998;121:561-579).

LANGUAGE IMPAIRMENT AND ARACHNOID CYSTS

Researchers at the Universite Catholique de Louvain, Brussels, Belgium, and Universite de Sherbrooke, Quebec, Canada studied 2 patients presenting with arachnoid cysts associated with cognitive impairment., particularly language impairment. Patient 1, a 6-year-old, right-handed boy had a large head, articulation and phonology anomalies, and a normal intelligence. MRI revealed a left temporal lobe arachnoid cyst, and PET scan showed decreased metabolism in the left superior temporal gyrus and thalamus. A 24 hour-EEG was normal. A cysto-peritoneal shunt was placed at age 6 years. Postoperative MRI, 2 months after surgery, showed disappearance of the cyst and full re-expansion of the temporal lobe parenchyma. PET at 21 months postoperatively revealed a normal symmetric temporal lobe signal. The boy's phonology improved and was normal at 12 months postoperatively. Neuropsychological assessment repeated from 6 to 70 months postoperatively revealed language and attention span improvements, and an increase in full-scale IQ from 93 to 112, with no learning disabilities evident.

Patient 2 , a 7-year-old, right-handed boy was admitted for chronic headaches of increasing intensity, associated with occasional vomiting. Neurologic exam was normal. Neuropsychological evaluation showed attention deficits, deficits in verbal comprehension, speech and syntactic, and in word definitions. Full scale IQ was normal. MRI at age 8 years showed a large arachnoid cyst at the base of the left sylvian fissure, causing a mass effect on the temporal lobe. 24 hour-EEG showed rare bursts of generalized spike and wave activity. A cysto-peritoneal shunt relieved the headaches and reduced the cyst volume. Postoperative EEG was similar to the original. Neuropsychological re-examination at 6 months showed improved verbal comprehension

and attention. IQ remained the same, with verbal IQ of 98 and performance IQ of 105. (Laporte N, De Volder A, Bonnier C, Raftopoulos C, Sebire G. Language impairment associated with arachnoid cysts: Recovery after surgical treatment. **Pediatr Neurol** Jan 2012;46:44-47). (Respond: Dr Sebire, E-mail: Guillaum.Sebire@USherbrooke.ca).

COMMENT. The authors consider the following as evidence of cause and effect between the surgery and cognitive improvement: 1) close temporal relationships; 2) PET increased metabolic activity in the affected temporal lobe after surgery; and 3) a correlation between the language impairment profiles and the location of the mass effect. A syndrome of temporal lobe arachnoid cyst and ADHD is further evidence supporting an association between these cysts and attention and behavioral disorders. Treatment is usually conservative, relying on medications, academic and behavioral modifications.

TRAUMATIC BRAIN DISORDERS

CEREBRAL BLOOD FLOW ALTERATIONS WITH CONCUSSION

Researchers at Cincinnati Children's Hospital Medical Center, OH evaluated 12 children, ages 11 to 15 years, following sports-related concussion (SRC), employing ImPACT neurocognitive testing, T1 and susceptibility weighted MRI, diffusion tensor imaging, proton MR spectroscopy, and phase contrast angiography at <72 hours, 14 days, and 30 days or greater. Findings were compared to an age and gender-matched control group. ImPACT confirmed significant differences between the SRC and control groups in initial total symptom score and reaction time. Total symptom score differences resolved by 14 days and reaction time by 30 days. MRI showed no structural injury. MR spectroscopy showed no decrease in neuronal metabolite N-acetyl aspartate or elevation of lactic acid. In contrast, reduction in cerebral blood flow (CBF) was documented in the SRC group (38 vs 48 ml/100 g/min, P=.027). Improvement in CBF toward control values occurred in only 27% of participants at 14 days and in 64% at >30 days after SRC. Pediatric SRC impairs CBF and produces a pathophysiologic process without causing structural or metabolic brain damage. Altered CBF may contribute to SRC-related symptoms and altered neurologic and neuropsychiatric function A prescription of cognitive rest in patients with reduced CBF is thought to promote recovery from SRC by reducing cerebral metabolic demand. (Maugans TA, Farley C, Altaye M, Leach J, Cecil KM. **Pediatrics** January 2012;129:28-37). (Respond: Todd Maugans MD, Division of Pediatric Neurosurgery, Cincinnati Children's Hospital Medical Center, MLC 2016, 3333 Burnet Ave, Cincinnati, OH 45229. E-mail: todd.maugans@cchmc.org).

COMMENT. Sports-related concussion in children may cause a significant reduction in cerebral blood flow without measurable structural or metabolic neuronal injury. These findings differ from adults who demonstrate cerebral metabolic changes following sports-related head trauma. (Vagnozzi R et al. **Brain** 2010;133(11):3232-3242, cited by authors). In the February issue of **Pediatrics** (2012;129(2):e494-5), Levin HS commenting on two current studies (Crowe LM et al and Anderson V et al) finds in children with TBI there are limits to neuroplasticity of the young brain and a high risk of persisting deficits. Children with early TBI do not "grow into their deficit."