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J. GORDON MILLICHAP, M.D., F.R.C.P., EDITOR

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MOVEMENT DISORDERS

DOPAMINE-SEROTONIN TRANSPORTER DISEASE

Investigators at the Hospital for Sick Children, University of Toronto, Canada report 8 children of a consanguineous Saudi Arabian family who had a similar movement disorder, with autosomal recessive inheritance and a mutation in the SLC18A2 gene that encodes vesicular monoamine transporter 2 [VMAT2]. VMAT2 translocates dopamine and serotonin into synaptic vesicles and is essential for motor control, stable mood, and autonomic function. The index patient had presented with hypotonia at 4 months of age, loss of acquired head control, episodes of oculogyric crisis, and slow development. She sat at 30 months and walked at 13 years. At 16 years of age, she had excessive diaphoresis, profuse nasal secretions, hypernasal speech, cold hands and feet, sleep disorder, and ataxia. Neurologic examination revealed ptosis, facial dyskinesia, impaired vertical gaze, and hand tremor. Gait was parkinsonian and dystonic. CSF showed normal levels of neurotransmitter metabolites, whereas urinary neurotransmitter tests revealed elevated levels of monoamine metabolites (5-hydroxyindoleacetic acid, homovanillic acid) and decreased levels of norepinephrine and dopamine. Treatment of the proband and 3 younger affected siblings with levodopa-carbidopa resulted in major immediate deterioration, with chorea and worsened dystonia. Rapid return to baseline function followed withdrawal of the medication. Immediate ambulation, near-complete resolution of the movement disorder, and improvement in development followed treatment with a direct dopamine-receptor agonist (pramipexole). The younger the affected child, the more substantial the recovery, and side effects after 32 months are minimal (overactivity and weight loss). (Rilstone JJ, Alkhater RA, Minassian BA. Brain dopamine-serotonin vesicular transporter disease and its treatment. **N Engl J Med** 2013 Feb 7;368(6):543-50). (Reprint requests: Dr Minassian. E-mail: berge.minassian@sickkids.ca).

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COMMENT. The monoamine neurotransmitter disorders are an expanding group of neurologic syndromes, usually diagnosed by measurement of neurotransmitter metabolites in the CSF. (Kurian MA, et al. **Lancet Neurol** 2011 Aug;10(8):721-33). Deficiency in dopamine is associated with movement disorder, deficient norepinephrine or epinephrine causes autonomic dysfunction, and serotonin deficiency results in sleep and psychiatric disorders. The members of the family described have symptoms of all neurotransmitter deficiencies but have no measurable deficiencies on CSF analyses. Symptoms result from impairment of synaptic transmission involving dopamine-serotonin vesicular transport and caused by a gene mutation. Whereas L-dopa treatment exacerbated symptoms, a direct dopamine agonist caused a reversal of symptoms.

Dopamine agonists (pramipexole, ropinirole) have a direct dopaminergic effect on striatal neurons and, in the treatment of Parkinson disease, they may have a modulating effect on L-dopa and are associated with fewer dyskinetic motor complications. As a substitute for L-dopa, dopamine agonists require further study. Dosage appears all important, even small doses when first introduced may cause orthostatic hypotension and unpredictable sleepiness in adults. (**Adams and Victor's Principles of Neurology**, 9th edition. Eds. Ropper AH, Samuels MA. New York, McGraw Hill Medical, 2009; 1041-42). Dopamine agonists have been used in the treatment of restless leg syndrome and are of benefit in the restoration of functional arousal, awareness, and communication in children following traumatic brain injury (Patrick PD et al. **J Child Neurol** 2006 Oct;21(10):879-85).

CHOREA ASSOCIATED WITH HHV-6 ENCEPHALITIS

Investigators at Brown University, Providence, RI and other centers in the US and Canada report a 14-month old child with multiple episodes of febrile status epilepticus, followed by chorea and developmental regression, caused by human herpes virus-6 encephalitis. Chorea and seizures resolved following treatment with levetiracetam, IV immunoglobulin, and foscarnet, but developmental regression with loss of language skills persisted at 6 months follow-up. This is considered a novel manifestation of HHV-6 encephalitis. (Pulickal AS, Ramachandran S, Rizek P, Narula P, Scubert R. Chorea and developmental regression associated with human herpes virus-6 encephalitis. **Pediatr Neurol** 2013 Mar;48(3):249-51). (Response: Dr Pulickal, Division of Neonatology, Alpert Medical School of Brown University, Women & Infants' Hospital, 101 Dudley Street, Providence, RI 02889. E-mail: apulickal@wihri.org).

COMMENT. HHV-6B is the cause of one third of all febrile convulsions in children under age 2 years in the United States (Hall CB, et al. **N Engl J Med** 1994 Aug 18;331(7):432-8), and a cause of mesial temporal lobe epilepsy after febrile status epilepticus (Theodore WH, Epstein L, Gaillard WD, et al. HHV-6B: a possible role in epilepsy? **Epilepsia** 2008 Nov;49(11):1828-37). Other disorders attributed to HHV-6 infection include meningoencephalitis, encephalopathy, demyelinating diseases, ataxia, opsoclonus-myoclonus, and cranial neuropathies. In addition to symptoms of involvement of the cerebral cortex, brain stem, cerebellum, spinal cord, hippocampus, and mesial temporal lobe, HHV-6 infection may also present with symptoms of basal ganglia virus involvement, either direct or autoimmune.

SEIZURE DISORDERS

CONCORDANCE OF MRI AND EEG FOCAL SLOWING IN NONSYNDROMIC EPILEPSY

Investigators at the Kangwon National University, Korea, and The Epilepsy Center, Lurie Children's Hospital of Chicago, USA studied the correlation and significance of EEG focal slowing and focal MRI abnormalities in 253 children with nonsyndromic epilepsy. EEG (n=5,149) and MRI (n=22,543) reports of patients seen at the Epilepsy Center, Chicago from 2000 to 2010 were reviewed initially by a computer-programmed keyword searching technique. Patients with nonsyndromic epilepsy were manually reviewed and divided into 4 groups: 1) focal slowing and no interictal epileptiform discharge (IED)(n=34); 2) focal IEDs and no focal slowing (n=84); 3) focal slowing and focal IED (n=102); and 4) normal findings (n=33).

MRI abnormalities were found in 59%, 56%, 74%, and 27% in groups 1, 2, 3, and 4, respectively ($p<0.0001$). Of children with nonsyndromic epilepsy and focal slowing, 70% had a brain MRI abnormality, and of those with focal IEDs on the EEG, 56% had an abnormal MRI. Focal slowing was not restricted to lesions involving cortical white matter only, but was often associated with lesions in multiple layers. One third of structural MRI abnormalities were diffuse, whereas the other two thirds were associated with a focal lesion. Of children with epilepsy and no focal EEG slowing, 20% had a focal structural MRI. In groups with focal slowing (1 and 3), cortical malformation (CM) was the most common pathology. Focal slowing correlated with the laterality of the MRI lesion in 61-70% cases, and with the location in 40%. Cortical malformation was 7 times more common than tumors in children with MRI lesions. Younger children have a higher percentage of cortical malformations whereas older children have a higher proportion of atrophy and tumors. Focal slowing, in addition to focal interictal epileptiform activity, is an important and useful EEG indicator of a brain structural abnormality in children with nonsyndromic epilepsy. (Noh BH, Berg AT, Nordli DR Jr. Concordance of MRI lesions and EEG focal slowing in children with nonsyndromic epilepsy. **Epilepsia** 2013 Mar;54(3):455-60). (Response: Dr Douglas R Nordli Jr, 225 E Chicago Ave, Epilepsy Box 29, Chicago, IL 60611, USA. E-mail: dnordli@luriechildrens.org).

COMMENT. Focal slowing in the EEG should be added to the guidelines for imaging children with epilepsy as outlined by Hirtz D, Ashwal S, Berg A, et al. (**Neurology** 2000 Sep 12;55(5):616-23) and by Gaillard WD, Chiron C, Cross JH, et al. (**Epilepsia** 2009 Sep;50(9):2147-53) as cited by the authors. The recommended guidelines are then as follows: 1) when localization-related epilepsy is known or suspected; 2) if epilepsy classification is in doubt; 3) when epilepsy syndrome with remote symptomatic cause is suspected; or 4) when focal slowing is recorded in the interictal EEG. The present study and report should serve to reinstate the utility and importance of the EEG in the localization and etiology of cerebral pathology. To quote Niedermeyer F (The clinical relevance of EEG interpretation. **Clin Electroencephalogr** 2003 Jul;34(3):93-8) of Johns Hopkins University, "There is need to re-emphasize the capabilities of electroencephalography -- the idea that EEG information is limited to epileptology and 'hunting spikes' is erroneous."

EPILEPTIFORM EEG DISCHARGES AND RISK OF EPILEPSY FOLLOWING FEBRILE SEIZURE

Investigators at Kangnam and Masan Samsung Changwon Hospitals, Korea, studied the relation between epileptiform discharges on the EEG after febrile seizures (FS) and the risk of developing epilepsy and recurrence of FS. Thirty-six children with FS and EEG epileptiform discharges were compared with a control group of 87 children with FS and normal EEG. The average age of the abnormal EEG group was higher than the control group (39.4 vs 25.9 months; $p<0.05$). First EEGs were obtained 4.4 and 4.5 days after the FS in study and control groups, respectively. Acute treatment with lorazepam was the same for both groups. FS were simple in 43% of the abnormal EEG group and 53% of the control group (NS). Complex FS occurred in 57% of the abnormal EEG group and 47% of the controls (NS). Recurrence rate of FS in patients with normal EEG (26.4%) was not significantly different from that in patients with FS and EEG showing epileptiform discharges (33.3%). Of patients with epileptiform discharges on EEG, 25% (9 of 36) had epilepsy compared to 2.3% (2 of 87) of children in the control group, and the difference was significant. EEG epileptiform discharges were focal spikes (central in 56%); none showed generalized spikes. Follow-up EEG in 19 patients (53%) with repeated febrile and unprovoked seizures was normal in 8 (32%) and showed persistent epileptiform discharges in 11 (68%). Neuroimaging studies in both groups were normal. Epileptiform discharges on the EEG of FS patients are a predictive risk factor of the development of epilepsy. (Wo SB, Lee JH, Lee YJ, Sung, T-J, Lee KH, Kim SK. Risk for developing epilepsy and epileptiform discharges on EEG in patients with febrile seizures. **Brain Dev** 2013 Apr;35(4):307-11). (Response: Dr Sung Koo Kim, Division of Pediatric Neurology, Kangnam Sacred Heart Hospital, Hallym University, Seoul 150-950, R of Korea. E-mail: pedkimsk@gmail.com).

COMMENT. In the current study, further analysis of the data reveals that the incidence of EEG showing epileptiform discharges in patients presenting with FS is 29% (36 of 123) and the incidence of epilepsy is 9% (11 of 123). Follow-up EEGs had persistent epileptiform discharges in 11 (68.4%) patients, and 8 (73%) of the 11 had recurrent unprovoked seizures. In a review of the literature from 1947 through 1964, the mean incidence of EEG epileptiform discharges in 23 published reports of children with FS was 25% (Millichap JG, et al. **Neurology** 1960 Jul;10:643-53; **Febrile Convulsions.** New York, Macmillan, 1968). In one early study (Lennox MA. **Proc Assoc Res Nerv Ment Dis** 1947;26:342-365) the incidence of epilepsy in patients with FS and paroxysmal EEGs was 53%. Since the incidence of abnormal EEGs was higher in older children, Lennox recommended repeated EEGs following a febrile seizure to determine the risk of development of epilepsy. Patients with pronounced slow frequencies in the EEG had a greater incidence of recurrent FS and paroxysmal abnormalities. EEG is rarely indicated following a simple FS but may be of predictive value in development of epilepsy following a complex, especially focal FS.

FRONTAL LOBE CONNECTIVITY AND COGNITIVE IMPAIRMENT IN FRONTAL LOBE EPILEPSY

Investigators at Maastricht University Medical Center, and Epilepsy Center Kempenhaeghe, The Netherlands, using functional magnetic resonance imaging (fMRI), studied the relationship between brain activation, functional connectivity, and cognitive functioning in 32 children aged 8-13 years with frontal lobe epilepsy (FLE) and 41 healthy age-matched controls. For the task-related fMRI, a Sternberg letter recognition task was used to induce cerebral activation, reflecting verbal working memory performance. Cognition was impaired in 16 children with FLE (50%) and in 3 healthy controls (7%). During working memory task performance, children with FLE showed a global decrease in functional brain connectivity compared to controls, whereas brain activation patterns remained intact. The widespread decrease in functional brain connectivity was similar in cognitively impaired and unimpaired patients. The decrease in frontal lobe connectivity in children with FLE complicated by cognitive impairment affected both connections within the frontal lobe and those from frontal to parietal and temporal lobes, cerebellum, and basal ganglia. The decrease in functional brain connectivity appeared to be related to the epilepsy itself, and was independent of cognitive performance.

The seizure types in this cohort of FLE patients were complex partial in 6 (19%), atypical absence in 13 (41%), and secondary generalized tonic-clonic in 5 (15%). The seizure focus based on EEG and history was bifrontal in 17 (53), left frontal in 8 (25%) and right frontal in 7 (22%). A history of febrile seizures was elicited in 9 (28%) and status epilepticus in 2 (6%). Seizures were refractory in 21 (66%). (Braakman HMH, Vaessen MJ, Jansen JFA, et al. Frontal lobe connectivity and cognitive impairment in pediatric frontal lobe epilepsy. **Epilepsia** 2013 Mar;54(3):446-54). (Response: Dr Hilde MH Braakman, Department of Neurology, Maastricht University Medical Center, The Netherlands. E-mail: hilde.braakman@gmail.com).

COMMENT. Impairment of functional integrity of the frontal lobe network in children with FLE extends to connections to temporo-parietal lobes, cerebellum and basal ganglia. The relation between these altered functional networks and cognition in FLE is unexplained. The authors refer to a literature review of pediatric FLE and to functional connectivity studies in adult patients with mesial temporal lobe epilepsy showing altered connectivity in network structures distant from the seizure focus (Waites AB et al. **Ann Neurol** 2006 Feb;59(2):335-43). (Braakman HMH, et al. Cognitive and behavioral complications of frontal lobe epilepsy in children: a review of the literature. **Epilepsia** 2011 May;52(5):849-56).

POPULATION-BASED STUDY OF EPILEPSY IN INFANTS

Investigators at the Paediatric Neurology Department, Great Ormond Street Hospital for Children, London, and other centers in the UK and USA carried out a population-based study of children, 1-24 months of age, with new-onset epilepsy, ascertained over 13 months from 15 boroughs of North London. A total of 57 children were enrolled, an incidence of 70.1/100,000 children <2 years of age/year; 23 (41%) were

White, 21 (37.5%) Asian, and 10 (18%) Black. The risk was highest among Asian infants ($p<0.001$). An electroclinical syndrome was identified in 24 (42%) cases of which 21 were epileptic encephalopathies (West [16], Ohtahara [2], and Dravet [3] syndromes). Overall, an underlying etiology for the epilepsy was identified in 29 children (51% of the cohort). Developmental brain abnormalities (polymicrogyria, tuberous sclerosis) were most frequent, occurring in 11 (21%), followed by acquired brain insults in 9 (16%) infants. Acquired causes included meningitis in 5 (9%), HIE in 4 (7%), and metabolic disorder in 4 (7%). Chromosomal abnormalities occurred in 4 (7%). MR images of 51 cases showed abnormalities in 37 (72%) and etiologically relevant abnormality in 26 (51%). (Eltze CM, Chong WK, Cox T, et al. A population-based study of newly diagnosed epilepsy in infants. **Epilepsia** 2013 Mar;54(3):437-445). (Response: Dr Christin M Eltze, Neurosciences Unit, UCL-Institute of Child Health, 4/5 Long Yard, London WC1N 3LU, UK. E-mail: c.eltze@ucl.ac.uk).

COMMENT. Infantile onset epilepsy frequently presents with intractable seizures and is commonly associated with diffuse encephalopathy, metabolic or structural brain abnormalities. Identification of specific electroclinical syndromes at seizure onset requires specialist intervention with video-EEG recordings, MRI, metabolic, and genetic studies. The EEG associated with an epileptic encephalopathy is diffusely abnormal and varies with cerebral maturation. (Nordli DR Jr. Epileptic encephalopathies in infants and children. **J Clin Neurophysiol** 2012 Oct;29(5):420-4). Details of EEG findings are important in the workup and in the classification of infantile seizures. Early referral of infantile seizure patients to a Pediatric Epilepsy Center is usually indicated for accurate seizure classification and optimal management. (Alam S, Lux AL. Epilepsies in infancy. **Arch Dis Child** 2012 Nov;97(11):985-92).

GENETICS OF BENIGN FAMILIAL INFANTILE EPILEPSIES

Investigators at Instituto G Gaslini, Genova, Italy and multiple other centers in Italy studied the genetics of benign familial epilepsies of the first year of life and assessed the extent of the genetic overlap between neonatal and infantile seizure syndromes. Families with at least two first-degree relatives affected by focal seizures with onset in the first year of life and normal development before seizure onset were included. A total of 46 families including 165 affected members were collected and were classified as benign familial neonatal seizures (BFNS) in 8 families, benign familial neonatal-infantile seizures (BFNIS) in 9 (1-4 months of age at onset), and benign familial infantile seizures (BFIS) in 29 (onset after 4 months of age in all family members). Genetic analysis identified 41 mutations, 14 affecting KCNQ2, 1 affecting KCNQ3, 5 affecting SCN2A, and 21 affecting PRRT2. The detection rate of mutations in this cohort was 89%. Mutations specifically involve KCNQ2 in BFNS, KCNQ2 (6 families) and SCN2A (two families) in BFNIS. BFIS families are most genetically heterogeneous, with all 4 genes involved, 70% carrying a PRRT2 mutation. PRRT2 mutations are clustered in families with BFIS and also, with paroxysmal kinesigenic dyskinesia.

KCNQ2 mutation is frequently represented in the entire spectrum of disorders, progressively decreasing with age, and may be predictive of afebrile seizures during follow-up, beyond the typical neonatal seizures. Age of onset of seizures is significantly

correlated with genetics: 90% of BFNS families are linked to KCNQ2 compared to only 3% of BFIS families. (Zara F, Specchio N, Striano P, et al. Genetic testing in benign familial epilepsies of the first year of life: Clinical and diagnostic significance. **Epilepsia** 2013 Mar;54(3):425-36). (Response: Dr Federico Zara. E-mail: federicozara@ospedale-gaslini.ge.it).

COMMENT. Mutational screening for neonatal and infantile seizures should involve KCNQ2 in both BFNS and BFNIS, and PRRT2 in BFIS families. A clear clinical classification of the seizure phenotype is an essential preliminary to genetic analysis. In addition to confirming a clinical diagnosis, a positive SCN1A mutation will influence treatment and improve seizure control. (Brunklaus A, et al. The clinical utility of an SCN1A genetic diagnosis in infantile-onset epilepsy. **Dev Med Child Neurol** 2013 Feb;55(2):154-61).

ANTIEPILEPTIC DRUGS AND DIET

FETAL AED EXPOSURE AND COGNITIVE OUTCOME AT AGE 6

Investigators at Emory University, Atlanta, GA and multiple centers in the USA and UK conducted a prospective study of the effects of antiepileptic drug (AED) monotherapy (carbamazepine, lamotrigine, phenytoin, or valproate) on the intelligence quotient (IQ) at 6 years of age (age-6 IQ). Of 305 mothers and 311 children (6 twin pairs) in the primary analysis, 224 children completed the 6 years of follow-up. Age-6 IQ was 7-10 points lower after exposure to valproate than to carbamazepine, lamotrigine, or phenytoin (p=0.0015, 0.0003, 0.0006, respectively). Measures of verbal and memory abilities were lower in children exposed to valproate compared to the other AEDs, and non-verbal and executive functions were lower with valproate compared to lamotrigine (but not carbamazepine or phenytoin). High doses of valproate were negatively associated with IQ, verbal ability, non-verbal ability, memory, and executive function; other AEDs were not. Age-6 IQ correlated with IQs at younger ages, and IQ improved with age for infants exposed to any AED. Right-handedness was less frequent overall and in the lamotrigine and valproate groups. Verbal abilities were lower than non-verbal abilities overall and in the lamotrigine and valproate groups. Mean IQs were higher in children exposed to periconceptual folate than in unexposed children (p=0.0009). (Meador KJ, Baker GA, Browning N, et al, for the NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. **Lancet Neurol** 2013 Mar;12(3):244-52). (Response: Prof Kimford J Meador, Dept of Neurology, Emory University, Atlanta, GA. E-mail: kimford.meador@emory.edu).

COMMENT. Fetal valproate exposure is associated with a range of cognitive deficits at 6 years of age, an effect dependent on the dose. IQ improves with age and with periconceptual folate. The authors hypothesize that a change in cerebral lateralization, with reduced right-handedness and lower verbal (vs non-verbal) abilities, may be caused by exposure to AEDs.

PUFAs, A DIETARY SUPPLEMENT AND SEIZURE THRESHOLD

Investigators at the University of Toronto, Canada studied the effects of chronic dietary supplementation with omega-3 polyunsaturated fatty acids (PUFAs) derived from fish oil on seizure thresholds in the amygdala as well as on blood and brain PUFA levels in 60-day-old rats. The acute effects of omega-3 PUFAs-eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were also tested in laboratory rats with experimental pentylenetetrazol seizures. Fish oil supplementation significantly increased amygdaloid afterdischarge thresholds after 3, 5, and 7 months treatment. Fish oil supplementation also increased serum EPA and DHA concentrations. DHA significantly increased the latency to seizure onset in the pentylenetetrazol seizure model, whereas EPA had no significant effect. (Taha AY, Trepanier M-O, Ciobanu FA, et al. A minimum of 3 months of dietary fish oil supplementation is required to raise amygdaloid afterdischarge seizure thresholds in rats – implications for treating complex partial seizures. **Epilepsy Behav** 2013 Apr;27(1):49-58). (Response: Dr Ameer Y Taha at National Institute on Aging, NIH, Bethesda, MD 20892. E-mail: a.taha@utoronto.ca).

COMMENT. Omega-3 PUFAs raise the seizure threshold in animals, but several months dietary supplementation may be required to demonstrate an effect in humans.

METABOLIC DISORDERS

MEDNIK SYNDROME: A DEFECT OF COPPER METABOLISM

Investigators at Bambino Gesu Children's Hospital, Rome, and other centers in Italy, Canada and France report an 8-year-old female Sephardic-Jewish patient with MEDNIK syndrome associated with a new AP1S1 homozygous mutation. She showed severe perturbations of copper metabolism with hypocupremia, hypoceruloplasminemia and liver copper accumulation with intrahepatic cholestasis. Treatment with zinc acetate resulted in improved clinical symptoms and liver copper metabolism. Reevaluation of 5 original French-Canadian patients with MEDNIK syndrome and AP1S1 mutations confirmed copper metabolism perturbation and hepatopathy in all patients. In the pathogenesis of MEDNIK syndrome, AP1S1 regulates intracellular copper machinery mediated by copper-pump proteins. This multisystem treatable disease combines clinical and biochemical signs of both Menkes and Wilson's diseases. (Martinelli D, Travaglini L, Drouin CA, et al. MEDNIK syndrome: a novel defect of copper metabolism treatable by zinc acetate therapy. **Brain** 2013 Mar;136(Pt 3):872-81). (Resp.: Dr Carlo Dionisi-Vici, Bambino Gesu Children's Hospital, Rome, Italy. E: carlo.dionisivici@opbg.net).

COMMENT. MEDNIK syndrome is an acronym for mental retardation, deafness, neuropathy, ichthyosis, and keratodermia, and is caused by AP1S1 gene mutations. This rare autosomal recessive neurocutaneous syndrome, first reported in French-Canadian families (Montpetit A, et al. **PLoS Genet** 2008 Dec;4(12):e1000296), is now known to be caused by a perturbation of copper metabolism, and is treatable with zinc acetate.