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

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SEIZURE DISORDERS

C-REACTIVE PROTEIN SERUM LEVELS AFTER SEIZURES

Investigators at Tampere University Hospital, Finland measured C-reactive protein (CRP) serum concentrations in 31 patients (mean age 34, range 6-58 years) with refractory focal epilepsy while undergoing video-EEG monitoring and compared with 80 healthy controls. CRP concentrations were significantly higher in patients with refractory focal epilepsy than in controls (3.5 vs 0.7 mg/ml, $p<0.001$). All 5 patients with elevated CRP had temporal lobe epilepsy (TLE)(i.e. 33% of 15 with TLE). None of 16 patients with extra-temporal lobe epilepsy had elevated CRP concentrations. Increase in CRP from baseline to a maximum level after the index seizure was dependent on the type of seizure ($p=0.005$). Secondarily generalized tonic-clonic seizure (SGTCS) was the most important predictor of increase in CRP level ($p=0.030$), whereas simple and complex partial seizures were without effect on CRP. SGTCS stimulates CRP production. Patients taking enzyme-inducing AEDs (carbamazepine or phenytoin) had higher levels of CRP than those on noninducing drugs ($p=0.084$, NS). Higher CPR levels were associated with lower numbers of AEDs ($p<0.001$), and were found in patients of older age at diagnosis and in measurements during the 24 hour video EEG ($p=0.003$). Baseline CRP level was not significantly associated with sex, etiology, seizure frequency, or duration of index seizure. Elevated levels of CRP in patients with refractory epilepsy emphasize the association between inflammation and epilepsy. These results suggest that a more severe seizure type (SGTCS) shows a stronger inflammatory response after an acute seizure. (Alapirtti T, Waris M, Fallah M, et al. C-reactive protein and seizures in focal epilepsy: a video-electroencephalographic study. **Epilepsia** 2012 May;53(5):790-796). (Respond: Dr Tiina Alapirtti, Department of Neurosciences and Rehabilitation, Tampere University Hospital, PO Box 2000, FI-33521, Tampere, Finland. E-mail: tiina.alapirtti@pshp.fi).

COMMENT. C-reactive protein (CRP) is produced by the liver in response to an

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inflammatory signal, most prominently interleukin-6 (IL-6). Blood levels of CRP may be used as a biomarker for inflammation, cardiovascular disease, dementia, and some epilepsies. The more severe the seizure, the stronger the inflammatory response and the higher the CRP level after an acute seizure. Epileptic seizures provoke a production of cytokines such as IL-6 that may in turn cause an activation of the acute phase reaction and elevation of blood CRP. (Peltola J et al. Indicators of inflammation after recent tonic-clonic epileptic seizures correlate with plasma interleukin-6 levels. **Seizure** 2002 Jan;11(1):44-46).

CELIAC DISEASE AND INCREASED RISK OF EPILEPSY

Researchers at Orebro University Hospital, Orebro, and the Karolinska Institute, Stockholm, Sweden; and the Universities of Naples and Salerno, Italy examined the risk of developing epilepsy in a nationwide population-based sample of >28,000 patients with biopsy-verified celiac disease (CD). The absolute risk of future epilepsy in patients with CD was 92/100,000 person-years (excess risk = 27/100,000 person-years), and the risk was independent of age. The hazard ratio (HR) for having at least 2 interactions with health care due to epilepsy was 1.41. In those patients with epilepsy treated with AEDs, the increased risk of epilepsy was 1.43. (Ludvigsson JF, Zingone F, Tomson T, Ekhom A, Ciaccio C. Increased risk of epilepsy in biopsy-verified celiac disease: A population-based cohort study. **Neurology** 2012 May 1;78:1401-1407). (Respond: Dr Ludvigsson. E-mail: jonasludvigsson@yahoo.com).

COMMENT. Celiac disease carries a moderately increased risk of epilepsy, and patients with epilepsy are at increased risk of future CD. The increased risk of epilepsy is present both before and after CD diagnosis, indicative of shared risk factors and supportive of an immunological etiology for epilepsy. (Vezzani A et al. The role of inflammation in epilepsy. **Nat Rev Neurol** 2011;7;31-40).

LONG-TERM EFFECTIVENESS OF ETHOSUXIMIDE, VALPROIC ACID AND LAMOTRIGINE IN ABSENCE EPILEPSY

Researchers at Seoul National University Bundang and Children's Hospitals, Republic of Korea evaluated the long-term effectiveness and tolerability of ethosuximide (ESX), valproic acid (VPA), and lamotrigine (LTG) as initial monotherapies for patients with childhood absence epilepsy (CAE). CAE was diagnosed according to the criteria of Panayiotopoulos (2005) in a total of 128 patients, female preponderance 1.8:1, and mean age at onset of 6.5 years; 48 were assigned to the ESX group, 59 were treated with VPA and 21 with LTG. The mean follow-up duration was 3.4 years (range, 1-17 years). ESX and VPA starting dose was 10 mg/kg/day, and 1 mg/kg/day for LTG. The final maintenance doses were 23 mg/kg/day for ESX, 26 mg/kg/day for VPA, and 4.7 mg/kg/day for LTG. The seizure-free rate of ESX at 3 months was 84% and significantly higher than that of VPA (62%) and LTG (54%). At 6 months, the seizure-free rate of ESX (90%) was significantly higher than that of LTG (63%); the seizure-free rates of VPA and LTG groups at 6 months were not significantly different. After 9 months, there was no significant difference in seizure-free rates among the 3 drug groups, nor in rates

of normalization of the EEG at 12 months (ESX, 77%; VPA, 83%; and LTG, 64%), retention rate through the treatment period, and adverse-event rates (ESX, 25%; VPA, 29%; and LTG, 14%). Frequent causes of AED withdrawal because of adverse events were GI complaints for ESX (10%), GI complaints (5%) and alopecia (7%) for VPA, and rash for LTG (5%).

ESX, VPA and LTG are equally effective in the long-term treatment of newly diagnosed CAE patients. The onset of efficacy is faster for ESX compared with VPA or LTG. (Hwang H, Kim H, Kim SH, et al. Long-term effectiveness of ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. **Brain Dev** 2012 May;34:344-348). (Respond: Dr Hee Hwang. E-mail: neuroandy@korea.com).

COMMENT. A previous double-blind, randomized, controlled clinical trial comparing the 3 drugs, ESX, VPA and LTG, found that ESX and VPA were more effective than LTG after 4-5 months of treatment. Attentional dysfunction was more common with VPA than with ethosuximide. (Glauser T et al. **N Engl J Med** 2010;362:790-799). The present study, extending the period of observation to 9 months, finds no significant difference in long-term effectiveness or adverse event rates of ESX, VPA and LTG. Apparently, contrary to earlier conclusions, "older (ESX) is not better!" (Vining EPG. **Pediatr Neurol Briefs** 2010 March;24(3):19).

YIELD OF ABNORMAL CT WITH FIRST COMPLEX FS

Physicians in Emergency Medicine, Pediatric Neurology, and Radiology at Children's Hospital Boston, MA studied the risk of intracranial pathology requiring immediate intervention among patients presenting in the ED with a first complex febrile seizure (CFS). Of a total of 526 patients identified with a first CFS between 1995 and 2008, 268 (50.4%) had emergent head CT imaging. Four patients had a clinically significant finding: 2 had intracranial hemorrhage, 1 had ADEM, and 1 had focal cerebral edema. The risk of intracranial pathology was 4 (0.8%). Three of the 4 had other obvious findings: nystagmus, emesis, altered mental status, persistent hemiparesis, bruises suggestive of inflicted injury. Patients presenting with more than one seizure in 24 hours are at very low risk. (Kimia AA, Ben-Joseph E, Prabhu S, et al. Yield of emergent neuroimaging among children presenting with a first complex febrile seizure. **Pediatr Emerg Care** 2012 April;28(4):316-321). (Response and reprints: Amit A Kimia MD, Division of Emergency Medicine, Children's Hospital Boston, 300 Longwood Ave, Boston, MA 02115. E-mail: amir.kimia@childrens.harvard.edu).

COMMENT. This study suggests that emergency neuroimaging may be unnecessary for children who present in the ED with a first CFS, uncomplicated by other acute signs of neuropathology. Focal and prolonged CFS may be more predictive of pathology than the multiple seizure type, especially when associated with prolonged postictal state.

In a retrospective study of 100 consecutive febrile seizure patient-visits to a university affiliated tertiary hospital, head CT was obtained in 18 patients at time of visit, with normal results in 17 (1 patient had mastoiditis). MRIs performed in 4 patients with CFS were normal. Of the 18 with CT scans, 4 had simple FS (5.8% of 77) and 14 had

CFS (60.9% of 23). None had neurological lesions requiring surgery. (Millichap JJ et al. Methods of investigation and management of infections causing febrile seizures. **Pediatr Neurol** 2008;39:381-386). CFS without neurologic signs of intracranial pathology is insufficient indication for emergent CT scan. Diagnostic criteria for CFS and indications for CT scan may require re-evaluation.

METABOLIC DISORDERS

COGNITIVE OUTCOME OF INFANTS WITH POMPE DISEASE RECEIVING ENZYME-REPLACEMENT THERAPY

Researchers at University Medical Center, Rotterdam, the Netherlands, and University of Leuven, Belgium prospectively assessed cognitive function in 10 children with classic infantile Pompe disease who had been treated with enzyme-replacement therapy (ERT) since 1999. Median age at diagnosis was 0.7 months (range 0.1-6.2 months). ERT was started at a median age of 2.3 months (range 0.1-8.3 months). Developmental scores in the first 4 years of life ranged from above average to severe delay. The type of IQ test used, severity of motor problems, speech/language delay, and age at start of ERT influenced the developmental scores. At young age poor motor functioning may interfere with reliable assessment of cognition. Scores in 5 children tested after 5 years of age ranged between normal and mild developmental delay. Nine children had hearing deficits and 7 had impaired vision. Brain imaging in 6 patients revealed periventricular white matter abnormalities in 4. (Ebbink BJ, Aarsen FK, van Gelder CM, et al. Cognitive outcome of patients with classic infantile Pompe disease receiving enzyme therapy. **Neurology** 2012 May 8;78:1512-1518). (Response and reprints: Prof van der Ploeg. E-mail: a.vanderploeg@erasmusmc.nl).

COMMENT. Pompe disease (glycogen storage disease type II; acid maltase deficiency) is an autosomal recessive, progressive metabolic myopathy due to lysosomal a-glucosidase deficiency. Enzyme activity is reduced to <1%, and glycogen stores accumulate in skeletal, cardiac, and smooth muscle, and in the brain. Pompe presents with neonatal hypotonia, macroglossia, cardiomegaly, and hepatomegaly. Patients usually die before 1 year of age with cardiorespiratory failure or aspiration pneumonia. ERT, using recombinant human a-glucosidase, improves motor development and lengthens life expectancy, but ERT does not cross the blood-brain-barrier. Glycogen is stored in the CNS and may cause cognitive deficits. This study shows that children treated with ERT who survive to school age may have normal to mildly delayed cognitive development. Testing of young children < 4 years is largely dependent on motor function. Since muscle involvement and weakness are prominent features of Pompe disease and are resistant to ERT, cognitive development will be underestimated in children younger than 5 years.

Early treatment and newborn screening for Pompe disease are recommended. (Chien YH et al. **Pediatrics** 2009 Dec;124(6):e1116-1125) (Burton BK. **Am J Med Genet C Semin Med Genet** 2012 Feb 15;160(1):8-12).

SEPIAPTERIN REDUCTASE DEFICIENCY: MIMIC OF CEREBRAL PALSY

Researchers at University of California at San Diego, and 22 other US national and international centers studied the clinical, biochemical, and molecular findings in a cohort of 38 patients with sepiapterin reductase deficiency (SRD). The phenotype and treatment response were assessed by chart and literature review. Average age of onset is 7 months, and delay to diagnosis is 9.1 years. Symptoms in infancy or childhood include motor and language delays, axial hypotonia, dystonia, weakness, oculogyric crises, with diurnal fluctuation, benefitted by sleep. Cerebral palsy is a common misdiagnosis. CSF showed low 5-hydroxyindoleacetic acid and homovanillic acid and elevated biopterin and sepiapterin. Diagnosis is confirmed by mutation analysis and/or enzyme activity in cultured fibroblasts. All patients treated with l-dopa in combination with carbidopa showed dramatic improvement. Early diagnosis and treatment are recommended. (Friedman J, Roze E, Abdenur JE, et al. Sepiapterin reductase deficiency: a treatable mimic of cerebral palsy. **Ann Neurol** 2012 April;71:520-530). (Respond: Dr Jennifer Friedman, Rady Children's Hospital, San Diego, 8010 Frost Street, Suite 400, San Diego, CA 92123. E-mail: jrfriedman@rchsd.org).

COMMENT. A diagnosis of SRD should be considered in patients with developmental delay, dystonia, axial hypotonia and atypical presumed cerebral palsy.

NEONATAL HYPOGLYCEMIA, LACTIC ACIDOSIS, AND PYRIDOXINE-DEPENDENT EPILEPSY

Researchers at the University of Toronto, Canada report the case of a 13-month-old girl with neonatal hypoglycemia, lactic acidosis, and bilateral symmetrical temporal lobe hemorrhages and thalamic changes on cranial MRI. She developed multifocal and myoclonic seizures refractory to multiple antiepileptic drugs that responded to pyridoxine. A diagnosis of a-aminoadipic semialdehyde dehydrogenase deficiency was confirmed by elevated urinary a-aminoadipic semialdehyde excretion, and a novel missense mutation in the *ALDH7A1* gene. Seizures were controlled by pyridoxine alone since 1.5 months of age. At 13 months, she has motor delay and central hypotonia but normal language and social development. (Mercimek-Mahmutoglu S, Horvath GA, Coulter-Mackie M, et al. Profound neonatal hypoglycemia and lactic acidosis caused by pyridoxine-dependent epilepsy. **Pediatrics** 2012 May;129:e1368-e1372).

COMMENT. Pyridoxine-dependent epilepsy is reported with mutations in the *ALDH7A1* gene that encodes antiquitin. The clinical spectrum of antiquitin deficiency includes ventriculomegaly detected on ultrasound, abnormal fetal movements, a multisystem neonatal disorder, and seizures and autistic features. Brain abnormalities and hypoglycemia that may coexist make diagnosis difficult, and tests for antiquitin deficiency and a clinical trial of pyridoxine are recommended when neonatal seizures are refractory to anticonvulsants. (Mills PB et al. **Brain** 2010 Jul;133(Pt7):2148-2159).

RISK PREDICTION FOR NIEMANN-PICK DISEASE

A retrospective chart review of 216 patients with Niemann-Pick disease type C (NP-C) was conducted in 5 centers in Europe including University of Amsterdam and 2 in Australia. Three patient types were selected: classic or variant filipin staining NP-C cases (n=71) including family members with NP-C, NP-C filipin-negative staining noncases (n=64), or controls with at least 1 characteristic symptom of NP-C (n=81). NP-C symptoms and signs were categorized into visceral, neurologic, or psychiatric domains. Logistic regression was performed on individual signs and symptoms within and across domains, and regression coefficients were used to develop prediction scores for NP-C.

The suspicion index tool has good discriminatory performance, and patients with a score >70 should be tested for NP-C. Strong predictors of NP-C are neonatal jaundice/cholestasis, splenomegaly, vertical supranuclear gaze palsy, cataplexy, and cognitive decline/dementia; also, symptoms occurring in multiple domains in individual patients, and parents/siblings or cousins with NP-C. (Wijburg FA, Sedel F, Pineda M, et al. Development of a suspicion index to aid diagnosis of Niemann-Pick disease type C. **Neurology** May 15;78(20):1560-1567). (Response and reprints: Dr Wijburg. E-mail: f.a.wijburg@amc.uva.nl).

COMMENT. NP-C is a rare inherited neurovisceral disease caused by mutations in the NPC1 (95%) or NPC2 gene (5% cases) that lead to accumulation of cholesterol and glycosphingolipids in the brain, liver and other tissues. Foamy cells are present in the bone marrow, spleen and liver, and sea-blue histiocytes in the bone marrow. Neurological manifestations include saccadic eye movement abnormalities or vertical supranuclear gaze palsy, cerebellar ataxia, dystonia, dysmetria, dysarthria and dysphagia, gelastic cataplexy, and seizures. Age at presentation is early-infantile, late infantile, juvenile or adolescent/adult. International guidelines for management of NP-C were published in 2009, updated 2011. Disease-specific therapy with miglustat is reevaluated. (Patterson MC et al. **Mol Genet Metab** 2012 May 7. Epub ahead of print).

Four varieties of NP disease are distinguished, ABC & D. Type A is the classic infantile neuronopathic form, presenting with failure to thrive, persistent neonatal jaundice, hepatomegaly, lymphadenopathy, and sometimes a retinal cherry red spot. It is more common in Ashkenazi Jewish families. Type D is found in Nova Scotian families.

AUTOIMMUNE AND DEMYELINATING DISORDERS

MYASTHENIA GRAVIS AND NEUROMYELITIS OPTICA ASSOCIATION

Investigators at the University of Oxford, UK and 8 other international neurology centers describe the clinical, serological, and temporal associations of myasthenia gravis (MG) and neuromyelitis optica spectrum disorder (NMOSD) in 16 patients. All had early onset acetylcholine receptor antibody [AChR-Ab]-mediated MG, the majority with mild generalized disease, and a high proportion achieved remission. The MG preceded

NMOSD by a median of 16 years, and 11 had thymectomy. Aquaporin-4 antibodies [AQP4-Ab] were detectable between 4 and 16 years prior to NMOSD onset. AChR-Abs decreased and the AQP4-Ab levels increased over time in concordance with MG and NMOSD, respectively. AChR-Abs were detectable at NMOSD onset in one of 2 patients diagnosed with NMOSD before MG. (Leite MI, Coutinho E, Lana-Peixoto M, et al. Myasthenia gravis and neuromyelitis optica spectrum disorder. A multicenter study of 16 patients. **Neurology** 2012 May 15;78:1601-1607). (Response and reprints: Dr Palace. E-mail: Jacqueline.palace@clneuro.ox.ac.uk).

COMMENT. The association of MG and NMOSD, 2 rare organ-specific autoimmune diseases mediated by 2 distinct antibodies, occurs more frequently than by chance. MG usually presents first, and respective antibodies are present years before onset of the relevant disease. The MG tends to be relatively mild and treatment responsive. Recent evidence suggests that the thymus is involved in both MG and NMOSD (Chan KH et al. **J Neuroimmunol** 2010;227:178-184; cited by authors). Given the risk of concurrent autoimmune diseases in patients with MG or NMO, routine evaluation of thyroid antibodies and AQP4-Abs may be considered in patients with early onset AChR-MG.

PROTEOMIC TECHNIQUES AS BIOMARKERS FOR MULTIPLE SCLEROSIS

Researchers at the Montreal Neurological Institute and other centers in Canada performed proteomics screening of CSF samples collected from 19 children at presentation of acquired inflammatory CNS demyelinating syndromes. Children were followed prospectively and 8 developed MS-defining recurrent disease activity (acquired CNS demyelinating syndrome [ADS]); 11 had no recurrent disease (ADS-monophasic) over a median period of 4.88 years (range, 2.52-6.12 years). Mass spectroscopy, peptide profiling, and quantitative immunoblotting were used to identify CSF proteins that might discriminate MS from monophasic demyelination.

Major compact myelin membrane proteins typically implicated in MS were not detected. Instead, multiple molecules that localize to the node of Ranvier and the surrounding axoglial apparatus membrane were increased by 10.2-fold in children subsequently diagnosed with MS. The CSF proteome signature obtained at the presentation of CNS inflammation may be predictive of subsequent MS diagnosis. (Dhaunchak AS, Becker C, Schulman H, et al on behalf of the Canadian Pediatric Demyelinating Disease Group. **Ann Neurol** 2012 May;71:601-613). (Respond: Dr Amit Bar-Or, Neuroimmunology, Montreal Neurological Institute, McGill University, 3801 University Street, Room 111, Montreal, Quebec, H3A284, Canada. E-mail: amit.bar-or@mcgill.ca).

COMMENT. In the same issue of the Annals, investigators from Japan report on the use of CSF proteomic pattern analysis to discriminate MS-related disorders in 107 adult patients. (Komori M et al. **Ann Neurol** 2012 May;71:614-623). An editorial (Bennett JL Owens GP. **Ann Neurol** 2012 May;71:587-588) comments that CSF proteomics is a promising window and biomarker for demyelinating disorders.

DEVELOPMENTAL DISORDERS

RHOMBENCEPHALOSYNAPSIS SPECTRUM OF SEVERITY

Investigators at University of Washington, Seattle, University of Southern California, and Children's Hospital Los Angeles evaluated neuroimaging findings in 42 patients (17 female, 25 male; age range, 2 days to 44 years) with rhombencephalosynapsis (RES). RES is defined as a partial or complete absence of the cerebellar vermis and midline fusion of the cerebellar hemispheres. A spectrum of RES severity is proposed, ranging from mild (partial absence of nodulus and vermis), to moderate (absence of posterior vermis) to severe (absence of posterior and anterior vermis), to complete (absence of entire vermis including nodulus). Severity of RES correlates with fusion of the tonsils, midbrain abnormalities including aqueductal stenosis and midline fusion of the tectum. RES is also associated with forebrain abnormalities including absent olfactory bulbs, dysgenesis of corpus callosum, absent septum pellucidum and rarely, atypical holoprosencephaly. In other patients with aqueductal stenosis at the U Washington, 9% were identified with RES. Subjects with more severe RES have more severe neurodevelopmental outcome. (Ishak GE, Dempsey JC, Shaw DWW, et al. Rhombencephalosynapsis: a hindbrain malformation associated with incomplete separation of midbrain and forebrain, hydrocephalus and a broad spectrum of severity. **Brain** 2012 May;135:1370-1386). (Respond E-mail: ishakg@u.washington.edu; ddoher@uw.edu).

COMMENT. RES occurs alone or in combination with other congenital malformations, such as Gomez-Lopez-Hernandez syndrome (RES plus parietal scalp alopecia, tower skull, and trigeminal anesthesia) and VACTERL (vertebral anomalies, anal atresia, cardiovascular anomalies, trachesophageal fistula, renal anomalies, and limb defects). Ataxia is the most frequent manifestation of RES, and cognitive outcome may be normal. A dorsal-ventral patterning defect is one hypothesis of the etiology (Sarnat HB. Molecular genetic classification of central nervous system malformations. **J Child Neurol** 2000;15:675-687). The cerebellar fusion is comparable with holoprosencephaly in the forebrain, an associated defect in some cases of RES. The absence of the vermis in RES may be compared also with Joubert syndrome (JS). The vermis in JS is shortened whereas in RES it is narrowed (Barth PG. **Brain** 2012 May;135:1346-1347).

Classification update of CNS malformations. Researchers at the University of California at San Francisco and international centers review and propose a modified classification of malformations of cerebral cortical development, common causes of neurodevelopmental delay and epilepsy. A major change in the group with cortical dysgeneses with abnormal cell proliferation is a new classification of focal cortical dysplasias (FCDs), a common cause of refractory epilepsy often amenable to surgery. (Barkovich AJ, Guerrini R, Kuzniecky RI, Jackson GD, Dobyns WB. A developmental and genetic classification for malformations of cortical development: update 2012. **Brain** 2012 May;135:1348-1369). (Respond: E-mail: james.barkovich@ucsf.edu).