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

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SEIZURE DISORDERS

LUMBAR PUNCTURE FOR FIRST SIMPLE FEBRILE SEIZURE

Compliance with American Academy of Pediatrics consensus statement recommendations regarding lumbar puncture for infants 6-18 months of age with a first simple febrile seizure was investigated by a retrospective review of 704 infants evaluated in the pediatric emergency medicine division at Children's Hospital Boston, MA, Oct 1995-Oct 2006. Immunization was up to date in 80% of 563 patients with recorded data. Lumbar puncture was performed for 271 (38%) of the children. CSF samples were available for 131 (70%) of 188 children 6-12 months of age and 129 (25%) of 516 children 12-18 months of age. Rates of lumbar puncture decreased significantly after 12 months of age and over time in both age groups ($P<0.001$). The proportion of patients, 6-12 months of age, with LP decreased from 100% (5 of 5) in 1995 to 22% (2 of 9) in 2006; in infants 12 to 18 months of age, the proportion with LP decreased from 71% (17 of 24) in 1995 to 5% (1 of 20) in 2006. No pathogen was discovered in CSF cultures. CSF white cell count was elevated in 10 patients, and a contaminant was identified in 10 cultures (3.8%). None of the 10 patients with CSF pleocytosis had bacteria isolated from blood cultures. No patient was diagnosed as having bacterial meningitis. Of 68 patients (10%) who had received antibiotics before the ED visit, 36 (53%) underwent LP, and 1 had CSF pleocytosis (9 WBCs/mm3, with 80% monocytes/lymphocytes). No pretreated child received a course of antibiotics as recommended for meningitis. The AAP consensus recommendation that clinicians strongly consider or consider LP for very young children with first simple febrile seizure has limited utility. The recommendations should be reconsidered and LP performed if there are clinical signs or symptoms of concern of meningitis. There is currently no evidence that a first simple febrile seizure represents any increase in risk for meningitis, compared with children in the

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same age group with fever but without febrile seizure. (Kimia AA, Capraro AJ, Hummel D, Johnston P, Harper MB. Utility of lumbar puncture for first simple febrile seizure among children 6 to 18 months of age. **Pediatrics** Jan 2009;123:6-12). (Respond: Amir 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. The AAP practice parameter emphasizes age as the main criterion for considering LP in young patients with first simple febrile seizure (AAP Practice parameter. **Pediatrics** 1996;97:769-772; discussion 773-775). In contrast, pediatric emergency medicine physicians consider symptoms of meningitis, independent of the seizure and fever, are required before LP is performed (Rosenberg NM et al. **Pediatr Emerg Care** 1992;8:300-301)(Nozicka C. **Pediatrics** 1997;99:306-307). A representative of the AAP committee responded that practice guidelines should not eliminate clinical judgment and are not mandatory (Duffner PK. **Pediatrics** 1997;99:306-307).

A recent 2008 report of patients with febrile seizures (FS) treated in a 1-year period, 2005-06, at an East Carolina University-affiliated hospital found that FS were first episodes in 64%, simple in 77%, and complex in 23%. At 100 consecutive FS patient visits, LP was performed in 14%; 11 had complex FS and 3 were simple FS (no SFS patient was aged <12 months and only 1 was aged <18 months). Of 49 patients with FSFS, only 3 (6%) underwent LP, and age (13 months) was an indication in 1. In a total of 77 patients with SFS, 3.9% underwent LP, compared with 48% of those with complex FS. (Millichap JJ et al. **Pediatr Neurol** 2008;39:381-386). All were negative for evidence of bacterial or viral meningitis. Age was not a prominent criterion for LP. Complex FS was the main criterion for LP. Other factors significantly more prevalent in patients with LP compared to those without were an abnormal neurological examination, and signs of infection prompting blood culture and empiric antibiotic treatment. In the year 2006, the proportion of patients aged 6-18 months with first SFS who received LP was 3.5% (1 of 28) in the East Carolina and 10% (3 of 29) in the Boston studies. The decision to perform LP based on clinical indications and the physician's judgment is supported by the findings and recommendations of both groups.

EFFECT OF FEBRILE SEIZURES ON OXIDANT STATUS

Erythrocyte malondialdehyde (EMA), glutathione peroxidase (GPO), and superoxide dismutase (SDM) levels were assessed in 31 children with a febrile seizure and 30 without, in a study at Dokuz Eylul University, Izmir, Turkey. Febrile seizures were simple in 25 (80%) and complex in 6 (20%) patients. EMA and GPO levels were significantly higher and SDM significantly lower in the febrile seizure group. Levels were not different in the simple and complex seizure groups. Changes in antioxidant enzyme levels are evidence of oxidative stress that may lead to brain cell damage following febrile seizures. (Gunes S, Dirik E, Yis U et al. Oxidant status in children after febrile seizures. **Pediatr Neurol** Jan 2009;40:47-49). (Respond: Dr Gunes, Department of Pediatrics, Dokuz Eylul University School of Medicine, 35340 Balcova, Izmir, Turkey. E-mail: sezgin_gunes@yahoo.com).

COMMENT. The authors conclude that the oxidant-antioxidant balance is disturbed in children with febrile seizures, and changes in lipid peroxidation and level of antioxidant

enzymes may result in neuronal cell damage after febrile seizures. That febrile seizures may be less benign than generally assumed, as suggested by this study, is also apparent from a recent report of MRI abnormalities that followed both simple and complex febrile seizures (Hesdorffer DC et al. **Epilepsia** 2008;49:765-771), and an increased risk of sudden unexpected death during 2 years after a first febrile seizure (Vestergaard M et al, **Lancet** 2008;372:457-463) (**Ped Neur Briefs** 2008;22:47-48 and 68-69). Recommendations for the management of febrile seizures are outlined in a report of the Italian League Against Epilepsy (**Epilepsia** Jan 2009;50(Suppl 1):2-6), with reference to the AAP Guidelines 1996, 1999, and to Fukuyama Y et al. **Brain Dev** 18:479-484. The possible benefits of prolonged antiepileptic therapy to prevent recurrence of febrile seizures must be weighed against the reported adverse cognitive effects. Currently, chronic prophylactic treatment is usually discouraged, except in some patients with recurrent complex febrile seizures. More effective antipyretic treatment, rapid viral testing and antiviral therapy should provide a more specific approach to the prevention of recurrence of febrile seizures (Millichap JJ et al. **J Infect Dis** 2008;198:1093-4).

RISK FACTORS FOR NEONATAL SEIZURES

The association between maternal characteristics and birth admission seizures in a cohort of 2.3 million California children born at >36 weeks' gestation between 1998 and 2002 was evaluated using database statistics at the University of California San Francisco and Davis, CA. The incidence of birth admission seizures was 0.95/1000 live births. The risk of seizures was higher in male infants. Women age 40 years and older who were nulliparous, had diabetes mellitus, intrapartum fever, or infection (chorioamnionitis) or delivered at >42 weeks had an increased risk of delivering an infant with seizures. Maternal/race ethnicity was significantly associated with seizures, with a lower risk in infants of Hispanic and Asian compared with Caucasian and African–American mothers. Identifying antenatal and intrapartum risk factors for neonatal seizures might lower infant neurological morbidity and mortality. Late delivery is one risk factor that might be avoided. (Glass HC, Pham TN, Danielsen B, Towner D, Glidden D, Wu YW. Antenatal and intrapartum risk factors for seizures in term newborns: a population-based study, California 1998-2002. **J Pediatr** Jan 2009;154:24-28). (Reprints: Hannah C Glass**,** University of California San Francisco, Department of Neurology Box 0663, 521 Parnassus Ave, C-215, San Francisco, CA 94143. E-mail: Hannah.Glass@ucsf.edu.).

COMMENT. Previous reports found a higher incidence of neonatal seizures, from 1 to 3.5 per 1000 in term infants, but other studies included seizures up to 28 days of life. The increased risk of seizures at birth with maternal intrapartum fever and infection remains elevated even when meningitis or neonatal infection is excluded. The risk is higher in febrile multiparous compared to nulliparous women. A higher risk of seizures in infants born by cesarean section during night hours is unexplained.

Unexplained seizures in an infant. A girl born by cesarean section at 38 weeks after placental detachment developed generalized tonic-clonic seizures and tremors at 2 months. Blood tests, EEG and MRI were normal. The mother was receiving amitriptyline for postnatal depression and tension headache. The infant was treated with phenobarbital but

seizures recurred, even during hospitalization. Metabolic studies were considered. At one hospital stay, the seizure was complicated by ventricular tachycardia and fibrillation. After transfer to intensive-care for resuscitation, she was comatose and hypotonic, her pupils were dilated but reactive, and she was ventilated mechanically. She rapidly recovered consciousness, breathed independently, and moved all limbs. Mother was unimpressed and denied improvement in her child's condition. Toxicological studies obtained because of mother's incongruous response disclosed serum concentrations of amitryptyline 350 mcg/L. Mother admitted that she had administered amitryptyline drops to the infant for the past month. When removed to live with maternal grandmother, the child remained well and without seizures. The child was a victim of the factitious disorder, Munchausen's syndrome by proxy (Astuto M et al. **Lancet** Jan 3, 2009;373:94).

MRI FINDINGS AND SEIZURE OUTCOMES COMPARED IN FOCAL CORTICAL DYSPLASIAS TYPES I AND II

Preoperative clinical, neuropsychological, EEG, and imaging features and surgical outcomes of focal cortical dysplasias (FCD) types I and II were compared in 40 children with refractory epilepsy and histopathologically confirmed FCD subtypes, in a study at Charles University, Prague, Czech Republic and centers in Germany. FCD type I was identified in 24 and FCD type II in 16 patients. Seizure types were secondarily generalized tonic-clonic in 54% of FCDI and 37% FCDII; and infantile spasms in 21% of FCDI and 12% FCDII patients. Status epilepticus occurred in 4% of FCDI and 12% of FCDII patients. Multilobar involvement was found in 92% patients with FCDI and in 50% of FCDII patients. FCD type I MRI findings include white matter signal changes on T2 images and/or FLAIR, and reduction of white matter volume. FCD type II MRI showed increased cortical thickness, transmantle sign, gray-white matter junction blurring, fluid-attenuated inversion recovery (FLAIR) and proton density (PD) gray and white matter signal changes. Hippocampal atrophy occurred in only 1 patient of each type. Patients with FCD type I showed EEG continuous slowing more commonly; they had lower IQ levels and more behavioral disorders. Postsurgical seizure freedom occurred in 21% FCD type I and in 75% FCD type II patients ($P<0.001$). (Krsek P, Pieper T, Karimeier A et al. Different presurgical characteristics and seizure outcomes in children with focal cortical dysplasia type I or II. **Epilepsia** Jan 2009;50:125-137). (Respond: Pavel Krsek MD PhD, Department of Pediatric Neurology, Charles University, Second Medical School, Motol University Hospital, V Uvalu 84, CZ 15006 Prague 5, Czech Republic. E-mail:pavel.krsek@post.cz).

COMMENT. FCD is reported in up to 25% of surgical patients with intractable epilepsy and 5-10% of epilepsies. FCD Ia and Ib, and FCD IIa and IIb are classified histopathologically. Type IIa is distinguished by dysmorphic, and IIb by balloon cells. FCD type I patients present within the first year of life, and have multilobar involvement, high seizure frequency, more complications, and a worse prognosis than FCD type II patients. FCDI is more frequently associated with mental retardation and behavioral disorders, more difficult to localize by EEG and MRI, and has less favorable surgical outcome. The authors consider surgery except for hemispherectomy is frequently palliative in FCDI cases. FCD type I should be considered a distinct entity.

MOVEMENT DISORDERS

TOURETTE SYNDROME, MOTOR CORTEX EXCITABILITY AND COMORBIDITY

Motor cortex excitability in 29 untreated adult Gilles de la Tourette syndrome (TS) patients was measured using transcranial magnetic stimulation in a study at the Institute of Neurology, London, UK, and University of Ulm, Germany. A group of comorbid TS and ADHD patients showed abnormalities of measures of motor cortex excitability, patients with uncomplicated TS had abnormal results in all measures except intracortical facilitation, and patients with comorbid TS and OCD had abnormal short-interval intracortical inhibition and thresholds but normal levels of intracortical facilitation and short latency afferent inhibition. TS with ADHD comorbidity is associated with more extensive changes in the excitability of motor cortex circuits than uncomplicated TS or TS+OCD. The phenotype of TS may be related to the extent of involvement of different neuronal circuits. (Orth M, Rothwell JC. Motor cortex excitability and comorbidity in Gilles de la Tourette syndrome. **J Neurol Neurosurg Psychiatry** Jan 2009;80:29-34). (Respond: Dr M Orth, Department of Neurology, University of Ulm, Germany. E-mail: michael.orth@uni-ulm.de).

COMMENT. Transcranial magnetic stimulation (TMS) is a non-invasive method of measurement of motor cortex excitability while awake. TMS studies have demonstrated alterations of motor cortex excitability in patients with TS, uncomplicated and in those with ADHD or OCD comorbidity. Involvement of different neuronal circuits may be correlated with various subtypes of TS, alone or comorbid with ADHD or OCD.

BEHAVIORAL DISORDERS IN CHILDREN WITH TOURETTE SYNDROME

The prevalence of comorbid neurobehavioral problems in 35 children and adolescents (31 [88%] boys; mean age 11.8 years) with Tourette syndrome (TS) was determined at a psychiatric clinic at Shiraz University of Medical Sciences, Hafez Hospital, Iran. Motor tics were blinking (54%), mouth (31%) and shoulder (31%) movements. Vocal tics were throat clearing and grunting. Coprolalia occurred in 9%. Comorbid disruptive behavior disorders were ADHD in 24 (68%); ODD (28%); and CD in 5.7%. TS+disruptive behaviors occurred in 71%, TS+anxiety disorders in 43% (OCD 26%), TS+mood disorders in 14%. TS patients without comorbidity were uncommon (2.9%), and less than previously reported. (Ghanizadeh A, Mosallaei S. Psychiatric disorders and behavioral problems in children and adolescents with Tourette syndrome. **Brain Dev** Jan 2009;31:15-19), (Respond: Dr Ahmad Ghanizadeh, Department of Psychiatry, Research Center for Psychiatry and Behavioral Sciences, Hafez Hospital, Shiraz, Iran. E-mail: ghanizadeha@hotmail.com).

COMMENT. Almost all patients with TS have some behavioral comorbid disorder. ADHD is the most common comorbid disorder, followed by ODD and OCD. Mood disorders are uncommon.

NEUROMUSCULAR DISORDERS

FETAL ACETYLCHOLINE RECEPTOR INACTIVATION SYNDROME AND MATERNAL MYASTHENIA GRAVIS

Three brothers with facial diplegia and a myasthenic mother are reported from McGill University, Canada; University of Oxford, UK; and Columbia University, New York. Mother developed myasthenia at 33 years of age, presenting with ptosis, facial weakness, generalized fatigue, and elevated AChR Ab (>1000; normal <0.4). Her symptoms improved following thymectomy, pyridostigmine, prednisone, and plasmapheresis. Subsequently, three successive pregnancies were complicated by polyhydramnios, and at birth the infants were hypotonic, had a poor suck, and swallowing difficulty. In the first pregnancy, mother received no plasmapheresis. The infant remained in the NICU with transient neonatal myasthenia gravis (TNMG) for 5 weeks and improved with IV immunoglobulin. At 5 years he has microcephaly, facial diplegia, excessive drooling, and hypernasal speech. Brain MRI, serum CK, and repetitive nerve stimulation are normal. In the second pregnancy, mother received plasmapheresis biweekly after the first trimester, but the infant developed TNMG and neurologic abnormalities, similar to the first infant. In the third pregnancy, mother received plasmapheresis biweekly throughout the pregnancy, and the infant was the least severely affected. He was hypotonic and sucked poorly at birth but he swallowed. He remained in the NICU with TNMG for 3 weeks, and improved with nasogastric tube feedings. At 2 years, he has mild facial diplegia, full mouth and eye closure, and mild speech difficulties. All 3 siblings have facial diplegia, incomplete mouth closure (see photo provided in article), high arched palate, excessive drooling, normal milestones of motor development, normal muscle strength, pes cavus deformities, areflexia, no arthrogryposis, surgically corrected cryptorchidism and inguinal hernias, and middle ear effusions with conductive hearing loss. Mother's serum obtained when asymptomatic after the third pregnancy was positive for AChR antibodies. The titer was 1,890 nM against fetal AChR and 157 nM against adult AChR (normal values <0.5 nM). More aggressive plasmapheresis during pregnancy correlates with decreasing phenotypic severity of this syndrome. (Oskoui M, Jacobson L, Chung WK et al. Fetal acetylcholine receptor inactivation syndrome and maternal myasthenia gravis. **Neurology** Dec 2008;71:2010-2012). (Reprints: Dr Darryl C De Vivo, 710 168th St, 2nd Floor, New York, NY 10032. E-Mail: dcd1@columbia.edu).

COMMENT. The authors comment that fetal AChR persists until 33 weeks gestation, when the fetal (g) subunit is replaced by the adult (e) subunit. Despite intrauterine exposure to AChR antibodies (AChR Ab), most infants of myasthenic mothers are asymptomatic. A higher ratio of fetal to adult AChR Ab antibodies can lead to neonatal transient myasthenia gravis in 10-15% of infants. The fetal AChR inactivation syndrome described in the 3 brothers results from inactivation of the fetal subunit during a critical period of fetal development. Mothers with a previously affected child have a 100% risk of recurrence with subsequent children. Infants with transient neonatal myasthenia gravis should be examined for speech impairment and hearing loss at follow-up. The term *transient* neonatal myasthenia gravis is not entirely appropriate for these patients.

CHRNE MUTATION AND CONGENITAL MYASTHENIA

The CHRNE e1293insG mutation was identified in 14 (60%) of 23 North African families with an early onset form of congenital myasthenic syndrome studied at centers in France, Tunisia, Algeria, and UK. The phenotypic expression was homogeneous with moderate hypotonia and oculobulbar involvement, mild and stable course, and good response to cholinesterase inhibitors. This mutation is thought to originate in an ancient single founder event in the North African population. (Richard P, Gaudon K, Haddad H, et al. The CHRNE 1293insG founder mutation is a frequent cause of congenital myasthenia in North Africa. **Neurology** Dec 1 2008;71:1967-1972). (Reprints: Dr Daniel Hantai, Inserm U582.47, Boulevard de l'Hopital, Paris, France 75651.
E-mail:d.hantai@institut-myologie.org).

COMMENT. Congenital myasthenic syndrome (CMS) is caused by various genetic defects that include recessive mutations in AChR subunit CHRNE gene. In North Africa, most patients are homozygous for the e1293insG mutation. In Europe, the mutation is associated with a heteroallelic mutation in CHRNE. The DOK7 mutation CMS has a broad clinical phenotype, distinguished by the absence of external ophthalmoplegia, a progressive deterioration of respiratory function, and lack of long-term response to esterase inhibitors (Muller JS et al. **Brain** 2007;30:1497-1506; **Ped Neur Briefs** June 2007;21:43-4). Molecular genetic testing is important in diagnosis and therapy of infants with CMS. In patients with COLQ mutations, esterase inhibitors may cause worsening of symptoms (**Ped Neur Briefs** March 2008;22:17-18). In an early report of 6 infants with a 'neonatal persistent (congenital) myasthenia gravis' treated at the Massachusetts General Hospital, Boston (Millichap & Dodge. **Neurology** 1960;10:1007-1014), mothers did not suffer from MG, but 2 cousins of 1 patient and a sister of another were affected. The principal presenting signs were ptosis, weak cry, and generalized weakness. In later childhood, ptosis and external ophthalmoplegia were most prominent, and involvement of bulbar musculature, weakness, and respiratory difficulty were uncommon and mild. Symptoms, especially ophthalmoplegia, were only partially relieved or refractory to pyridostigmine. In the MGH series of pediatric myasthenic patients, 10 infants had the neonatal transient type, 6 a congenital type, and 35 the juvenile type.

LANGUAGE DISORDERS

AUTOSOMAL DOMINANT PARTIAL EPILEPSY WITH AUDITORY FEATURES

Auditory and language processing in 17 subjects with autosomal dominant partial epilepsy with auditory features (ADPEAF) was investigated by MRI, fMRI, and MEG and compared to 26 controls, in a study at Columbia University, New York. Age of seizure onset was late childhood or adolescence. MRI revealed no structural abnormality, but fMRI and

MEG showed reduced or delayed activation patterns in affected subjects. A previous report of a lateral temporal malformation in ADPEAF is not supported by this study, but the findings point to a functional impairment of language processing. (Ottman, R, Rosenberger L, Bagic A, et al. Altered language processing in autosomal dominant partial epilepsy with auditory features. **Neurology** Dec 9 2008;71:1973-1980). (Reprints: Dr Ruth Ottman, GH Sergievsky Center, Columbia University, 630 West 168th Street, P&S Box 16, Ne York, NY 10032. E-mail: ro6@columbia.edu).

COMMENT. Autosomal dominant partial epilepsy with auditory features is an idiopathic focal epilepsy syndrome with auditory symptoms or receptive aphasia. Families with this syndrome commonly have mutations in the LGI1 gene. These authors previously published a review of the genetics of 24 ADPEAF families with mutations in the LGI1 gene (**Ped Neur Briefs** Sept 2008;22:71).

PROGNOSIS OF LANDAU-KLEFFNER SYNDROME

The long-term follow-up of seven patients with Landau-Kleffner syndrome (LKS) is reported from State University of Campinas, Brazil. All were males between age 8 and 27 years. Parents or patients were interviewed 3 to 16 years after disease onset. All had normal MRIs. All had interictal seizure discharges on the EEG, maximal on the temporal lobes in 5, and exacerbated in sleep. Age of disease onset was 3 to 9 years; 5 patients presented with seizures and 2 with language disorder. Seizures were focal motor in 6 patients; 3 had clonic orofacial movements, 2 had secondarily generalized seizures. Language disorder was insidious in onset in 4 and abrupt in 3. All patients had aphasia and verbal auditory agnosia. Two patients still had seizures at follow-up at 12 and 27 years of age, despite several antiepileptic drugs; seizures had resolved in 4. Language disorder had persisted in 3, it was partially in remission in 3, and had resolved in 1. Duration of aphasia was 2 to 8 years. One of 4 adult patients is employed, and 3 do not work independently. Three patients are under 13 years of age. Six of 7 patients have severe deficits in communication, and 3 have behavior problems. Only one patient has a normal quality of life. In six with limitations, aphasia/agnosia is the main problem. Shorter duration of aphasia correlates with better outcome. Five patients have normal EEGs, 6-17 years after disease onset; 2 still have abnormal EEGs and refractory seizures. (Duran MHC, Guimaraes CA, Medeiros LL, Guerreiro MM. Landau-Kleffner syndrome: Long-term follow-up. **Brain Dev** Jan 2009;31:58-63). (Respond: Dr MM Guerreiro. E-mail: mmg@fcm.unicamp.br).