PEDIATRIC NEUROLOGY BRIEFS
A MONTHLY JOURNAL REVIEW

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

Vol. 26, No. 10 October 2012

INFECTIOUS DISORDERS

LONG-TERM OUTCOME OF LYME NEUROBORRELIOSIS

Researchers at Falun General Hospital and other centers in Sweden determined the long-term neurologic outcome of 84 children with confirmed Lyme neuroborreliosis (LNB). A neurologic re-examination at a mean age of 13 years and a median follow-up of 5 years after diagnosis found a total recovery rate of 73% (n=61). None had progressive neurologic symptoms. Definite sequelae (objective neurologic findings) were found in 16 (19%) patients, and possible sequelae (nonspecific signs related in time with LNB diagnosis) in 7 (8%). Sequelae were motor in 8 patients, sensory in 8, and both motor and sensory in 7. Eleven (21%) of 53 patients with acute facial nerve palsy at diagnosis had moderate persistent facial palsy at follow-up. Persistent neuropathy was diagnosed in 1 patient, trigeminal neuropathy in 1, hemiparesis following an LNB stroke in 1, polyneuropathy in 1, and peroneal nerve palsy in 1. Romberg test was positive in 3 patients, and vertigo occurred in 1. Fine motor incoordination with dysgraphia was diagnosed in 3. Possible sequelae in 7 patients included paresthesia, pain, and imbalance. Impaired school performance and daily activities affected 37% of children with definite sequelae, 57% of the possible sequelae group, and 15% of the no sequelae group. Nonspecific subjective symptoms, including headache, fatigue, and memory or concentration difficulties, were similar in the 3 patient groups and a control group of 84 children. Age, gender, duration of symptoms at diagnosis, and antibiotic treatment did not differ significantly in patients with or without sequelae. (Skogman BH, Glimaker K, Nordwall M, Vrethem M, Odkvist L, Forsberg P. Long-term clinical outcome after Lyme neuroborreliosis in childhood. **Pediatrics** 2012 Aug;130(2):262-9). (Respond: Barbro H Skogman MD PhD, Center for Clinical Research in Dalarna (CKF), Nissersv 3, SE-791 82 Falun, Sweden. E-mail: barbro.hedinskogman@itdalarna.se).

PEDIATRIC NEUROLOGY BRIEFS © 1987-2012, ISSN 1043-3155 (print) 2166-6482 (online), is published monthly and covers selected articles from the world literature. The editor is Pediatric Neurologist at the Ann & Robert H. Lurie Children's Hospital of Chicago; Professor Emeritus, Northwestern University Feinberg School of Medicine. PNB is a continuing education service designed to expedite and facilitate the review of current scientific information for physicians and other health professionals. Apply to PediatricNeurologyBriefs.com for Subscriptions (12 issues, January - December 2012): Digital PDF, $72 (Residents/Fellows $36); Print + Digital, $96 within US & UK; $128 outside US & UK. Institutional rates are available. To order by mail: Pediatric Neurology Briefs Publishers, PO Box 11391, Chicago, IL 60611

COMMENT. Acute facial nerve palsy is a common symptom of LNB, and a significant number (21%) will persist at follow-up. In a previous study of long-term outcome (3-5 years) of facial palsy in LNB, one-half of patients with subjective symptoms of residual facial palsy had signs of mild to moderate dysfunction on clinical examination, III-IV on the House-Brackman grading scale (I normal-VI no movement). (Bagger-Sjoback D et al. **Otol Neurotol** 2005 Jul;26(4):790-5). Subjective symptoms, objective signs, and neurophysiological test results show no clear correlation.

Since LNB is amenable to antibiotic treatment, a high index of suspicion and early diagnosis of acute neurologic complications is important. Examples of more common neurologic manifestations include, in addition to facial palsy, lymphocytic meningitis, mononeuropathy multiplex, and painful radiculoneuritis. (Halperin JJ. **Curr Infect Dis Rep** 2011 Aug;13(4):360-6).

SPINAL TUBERCULOSIS (POTT'S DISEASE)

Researchers at Great Ormond Street Hospital for Children and Institute of Child Health, London, UK reviewed their experience of childhood spinal tuberculosis (TB) over a 15-year period (1995-2010). Of 21 patients identified (median age 9.7 years, range 3.4-15.9 years) 11 were Black African, 7 Asian, 2 Middle Eastern and 1 Caucasian. Nine were born in the UK, 1 in the Netherlands and the remainder outside Europe. Ten had traveled to a country endemic for TB within the year before diagnosis. Four (19%) had a previous diagnosis of TB, 11 (52%) a known contact, 10 (48%) had received BCG vaccine and none was HIV-positive. Clinical presentations included systemic symptoms in 18 (night sweats, weight loss, fever and anorexia), back pain in 16, neurological symptoms in 12 (weakness and limp in 7, sensory change in 5), and spinal deformity in 5. *Mycobacterium tuberculosis* was isolated in 14 patients (67%) by vertebral biopsy or from paraspinal abscess. Spinal cord compression or stenosis occurred in 8 (38%), vertebral collapse in 13 (62%), and paraspinal abscess in 15 (71%). Chest x-ray showed TB lung disease in 8 patients (38%). Extra-spinal disease was co-existent in 12 (57%) patients, including psoas abscess in 5 (24%). All patients received TB treatment for at least 12 months, 7 underwent surgery, and 75% resolved fully. All patients were alive and without neurologic deficit at a median follow-up of 24 months. (Eisen S, Honywood L, Shingadia D, Novelli V. Spinal tuberculosis in children. **Arch Dis Child** 2012 Aug;97(8):724-9). (Respond: Dr Sarah Eisen, Department of Infectious Diseases and Microbiology, Institute of Child Health, 30 Guildford St, London WC1N 1EH, UK. E-mail: saraheisen@hotmail.com).

COMMENT. The authors list key features that should alert the clinician to a diagnosis of spinal TB: TB contact or travel to endemic area, history of previous TB, systemic symptoms, back pain and long duration of symptoms. Treatment should be supervised closely and prolonged. Late onset paraplegia, a feature of Pott's disease, was not a complication in the authors' cases. In a series of 8 patients with late onset Pott's paraplegia due to kyphosis, this complication was treated successfully with decompression and grafting. A mean period of 24 years (range, 9-46 years) had elapsed from the onset of active disease and the age at neurological deterioration. (Bilsel N, et al. **Spinal Cord** 2000 Nov;38(11):669-74). This report re-emphasizes the need for long-

term antibacterial therapy, careful follow-up and monitoring with spinal x-ray and neurologic evaluation, as indicated in the Great Ormond Street experience of spinal TB.

METABOLIC DISORDERS

CLINICAL CHARACTERISTICS OF 5 PHENOTYPES OF COENZYME Q10 DEFICIENCY

Researchers at Columbia University Medical Center, New York; University of Genoa, Italy; and University of Granada, Spain reviewed 149 cases of coenzyme Q10 (ubiquinone) deficiency, including their own cohort of 76 patients diagnosed from 1997-2010. Cerebellar ataxia was the principal phenotype and the presenting symptom in 94 children (63%). Less frequent phenotypes included encephalomyopathy in 4 patients, isolated myopathy in 14, infantile-onset multisystemic disease in 17, nephropathy (with or without sensorineural hearing loss) in 11, and atypical presentations in 9. Other manifestations include neuropathy, seizures, congenital hypotonia, dystonia, ophthalmoplegia, retinitis pigmentosa, optic atrophy, agenesis of corpus callosum, and hypogonadism. Onset was primarily in childhood; 82% were aged < 13 years including 23% in infancy (<12 months). Mortality rate was 8%.

Direct measurement of CoQ10 in skeletal muscle by liquid chromatography is the most reliable test for diagnosis of CoQ10 deficiency. Morphological and biochemical findings differ in the various clinical forms. Family history suggests autosomal recessive inheritance. Pathogenic mutations are described in patients with the infantile multisystemic syndrome and some juvenile-onset cerebellar ataxia cases. Response to oral supplementation with CoQ10 is frequent but variable; one patient with infantile spasms failed to respond. (Emmanuele V, Lopez LC, Berardo A, et al. Heterogeneity of coenzyme Q10 deficiency. Patient study and literature review. **Arch Neurol** 2012 Aug;69(8):978-83). (Respond: Michio Hirano MD, H Houston Merritt Clinical Research Center, Department of Neurology, Columbia University Medical Center, 630 W 168th St, P&S 4-423, New York, NY 10032. E-mail: mh29@columbia.edu).

COMMENT. The occurrence of primary and secondary CoQ10 deficiencies adds to the difficulty in study of the molecular classification of this heterogeneous disorder. (Quinzii CM, Hirano M. **Biofactors** 2011 Sep;37(5):361-5). Pathogenic mutations are identified in genes involved in the biosynthesis of CoQ10 (primary CoQ10 deficiencies) or in genes not directly related to CoQ10 biosynthesis (secondary CoQ10 deficiencies). Respiratory chain defects may contribute to the pathogenesis of primary CoQ10 deficiencies.

HEADACHE DISORDERS

MANIFESTATIONS OF FAMILIAL HEMIPLEGIC MIGRAINE

Researchers at University of Arkansas, Little Rock, AR report 3 cases of familial hemiplegic migraine complicated by reversible cerebral edema and followed by

neurocognitive impairment. Patient 1, a 13-year-old girl developed a severe headache during a volleyball game and on neurologic examination she had global aphasia, right-sided weakness, and ataxia. The initial MRI was normal, but the initial EEG revealed generalized slowing, 1-2 Hz, in the left hemisphere. Follow-up MRI 9 days after onset of signs revealed increased T2 signal involving the left hemisphere, with mild mass effect and midline shift. Her mother and brother had frequent migraine episodes accompanied by confusion, aphasia and hemiplegia. Treatment included verapamil, valproic acid, methylprednisolone, and IV immunoglobulin. The diagnosis of familial hemiplegic migraine was supported by CACNA1A gene mutations. She was maintained without further migraine episodes while taking verapamil as prophylactic. MRI and EEG repeated at 4 months follow-up were normal, but she had attention and memory problems in school. Two male patients, ages 8 and 15 years, with similar histories to that of case 1 had EEGs that revealed slowing in one hemisphere, 1-2 Hz, consistent with the MRI finding of unilateral cerebral edema. Mutation was located on ATP1A2 gene in case 2, and gene mutation was lacking in case 3; minor head trauma may have precipitated this patient's migraine attack. Neuropsychological evaluation and/or school reports at follow-up revealed cognitive impairment, memory and attention problems in all 3 patients. (Asghar SJ, Milesi-Halle A, Kaushik C, Glasier C, Sharp GB. Variable manifestations of familial hemiplegic migraine associated with reversible cerebral edema in children. **Pediatr Neurol** 2012 Sep;47(3):201-4). (Respond: Dr Asghar, Section of Pediatric Neurology, University of Arkansas Children's Hospital, Little Rock, AR 72202. E-mail: asgharsheilaj@uams.edu).

COMMENT. Genetic heterogeneity and persistent cognitive impairment are illustrated by these case reports of variable manifestations of familial hemiplegic migraine. EEG slowing was consistent with the temporary cerebral edema as a feature of FHM. A triad of prolonged hemiplegic migraine, cerebellar ataxia, and epileptic seizures is linked to CACNA1A gene mutations and may be complicated by status epilepticus. (Zangaladze A et al. **Epilepsy Behav** 2010 Feb;17(2):293-5). This report recommends that patients with prolonged hemiplegic migraine attacks and confusion be tested with continuous EEG to rule out electrographic status.

Sporadic hemiplegic migraine presenting as acute encephalopathy. A 10-year-old boy with psychomotor delay and cerebellar vermis atrophy developed right hemiplegia with vomiting, loss of consciousness, convulsions, and fever. EEG showed delta activity over the left hemisphere, and MRI revealed swelling of the left temporo-occipital cortex. Interleukin-6 was elevated in the CSF. Acute symptoms resolved after 3 weeks and recurred 7 months later with migraine attacks. A de novo mutation in the CACNA1A gene was identified. Family history was negative for migraine. Both familial and sporadic hemiplegic migraines are genetically heterogeneous, the majority caused by CACNA1A mutations. (Ohmura K, et al. **Brain Dev** 2012 Sep;34(8):691-5).

SEX DIFFERENCES IN BRAIN OF MIGRAINEURS

Researchers at Children's Hospital Boston and other Harvard Medical School centers studied alterations in brain structure in male and female age-matched interictal

(migraine free) migraineurs and controls, using high-field MRI. Female migraineurs had thicker posterior insula and precuneus cortices and functional differences in response to noxious stimuli compared with male migraineurs and healthy controls of both sexes. Female migraineurs show greater activation in brain regions involved in emotional processing: amygdala, parahippocampus, basal ganglia and posterior cingulate cortex. (Maleki N, Linnman C, Brawn J, Burstein R, Becerra L, Borsook D. Her versus his migraine: multiple sex differences in brain function and structure. **Brain** 2012 Aug;135(Pt 8):2546-59). (Respond: Nasim Maleki PhD, Department of Anesthesia, Children's Hospital Boston, Harvard Medical School, Boston, MA 02115. E-mail: nasim.maleki@childrens.harvard.edu).

COMMENT. These findings may be important in therapy of migraine and development of specific drugs for female migraineurs, targeting stress related disorders. *Papez' circuit*, a major pathway of the limbic system that controls emotion, is involved in female migraine. The initial description of the pathway by Papez is as follows: hippocampal formation, fornix, mammillary bodies, mammillothalamic tract, anterior thalamic nucleus, internal capsule, cingulate gyrus, parahippocampal gyrus, entorhinal cortex, hippocampus. The prefrontal cortex and amygdala were included later in a larger loop or "circuit of emotion." (Eggers AE. Redrawing Papez' circuit: a theory about how acute stress becomes chronic and causes disease. **Med Hypotheses** 2007;69(4):852-7).

Therapeutic strategies in migraine patients with mood and anxiety disorders list amitriptyline, flunarizine, pregabalin, valproate, topiramate, and lamotrigine (for migraine with aura). (Finocchi C, et al. **Neurol Sci** 2010 Jun;31 Suppl 1:S95-8).

SEIZURE DISORDERS

OUTCOME OF THERAPIES IN REFRACTORY CONVULSIVE STATUS EPILEPTICUS

Researchers at Queen Square, London, review the long-term outcome of therapies in refractory convulsive status epilepticus. Of 596 patients reported (51% of the total of 1168). 201 (35%) died, 79 (13%) had severe neurological deficit, 80 (13%) mild neurological deficit, 22 (4%) with undefined deficit, and 208 (35%) recovered to baseline. The quality of reported outcome data is generally poor, and only broad recommendations for optimal therapy are possible. General anesthesia remains the backbone of therapy, and immediate control is achieved in two-thirds of cases. Agents analyzed include thiopental/pentobarbital, midazolam, propofol, and ketamine, each having advantages and disadvantages. Children are least likely to be treated with propofol because of risk of propofol infusion syndrome, with myocardial failure and high mortality on prolonged infusion. Ketamine is a second-line drug with potential neurotoxic effects. First-line anesthesia therapy should be used with intensive care support and treatment of the underlying cause. Second-line therapies include hypothermia, magnesium and pyridoxine infusions, immunological therapy, ketogenic diet, and neurosurgery. Antiepileptic drug therapy should be used concurrently with anesthesia but outcome data are sparse. Choice of drug regimens include polytherapy with 2 antiepileptic drugs, high-dose, avoid frequent switching, drugs with low interaction

potential, predictable kinetics, drugs without renal or hepatic toxicity, and avoidance of GABAergic AEDs. (Shorvon S, Ferlisi M. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. **Brain** 2012 Aug;135(Pt 8):2314-28). (Respond: Dr Simon Shorvon, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK. E-mail: s.shorvon@ucl.ac.uk).

COMMENT. The authors comment that the most striking conclusion of their review of literature was the poor quality of outcome data. Only broad recommendations were possible from the analysis of reports. Refractory status epilepticus is heterogeneous and prognosis depends on factors other than treatment, such as age and etiology. General anesthesia is generally effective, and the rate of withdrawal seizures is lower than often quoted. Propofol infusion syndrome is a rare but frequently fatal complication caused by impaired fatty acid oxidation. The hallmarks are metabolic acidosis, lipemia, rhabdomyolysis and myocardial failure. A 10-year-old boy with status epilepticus treated with propofol developed fatal propofol infusion syndrome when a ketogenic diet was initiated. (Baumeister FA, et al. **Neuropediatrics** 2004 Aug;35(4):250-2).

LONG-TERM OUTCOME IN JUVENILE MYOCLONIC EPILEPSY

Researchers at University of Greifswald, Germany; and Cleveland Clinic, OH, studied the long-term seizure outcome in patients with juvenile myoclonic epilepsy (JME) and identified factors predictive of seizure remission. Of 31 patients followed for at least 25 years (mean 39.1 years), 21 (67.7%) were seizure-free, and 6 (28.6%) had AEDs discontinued. Significant predictors for a poor long-term seizure outcome included occurrence of generalized tonic-clonic seizures (GTCS) preceded by bilateral myoclonic seizures ($p=0.03$), long duration of drug refractory epilepsy ($p=0.022$), and AED polytherapy ($p=0.023$). Complete remission of GTCS with AED significantly increases the chance for complete seizure freedom ($p=0.012$). Photoparoxysmal responses significantly increase risk of seizure recurrence after AED discontinuation ($p=0.05$). Long-term seizure freedom in two thirds of patients and validation of outcome predictors should permit clinicians to provide patients with a more favorable potential response to treatment. (Geithner J, Schneider F, Wang Z, et al. Predictors for long-term seizure outcome in juvenile myoclonic epilepsy: 25-63 years of follow-up. **Epilepsia** 2012 Aug;53(8):1379-86). (Respond: Dr Felix Schneider, Department of Neurology, Epilepsy Center, University of Greifswald, Sauerbruchstrasse, 17489 Greifswald, Germany. E-mail: felix.schneider@uni-greifswald.de).

COMMENT. A previous long-term study of JME in 24 patients, 25.8 years after seizure onset, found that 11 (48%) had discontinued treatment and 6 (25%) were seizure-free without AEDs for 5-23 years. (Camfield CS, Camfield PR. **Neurology** 2009 Sep 29;73(13):1041-5). Contrary to current opinion, these reports show that continuation of AED therapy in JME is not required in all patients, and predictive factors for long-term management and outcome are now available.

ETIOLOGY AND PROGNOSIS OF NEONATAL CONVULSIONS

Researchers at Istanbul University, Turkey evaluated etiologic and risk factors affecting long-term neurologic outcome in newborns with neonatal seizures. Of 112 newborns referred to the Department of Pediatric Neurology from Jan 1, 2007-Dec 31, 2009, 33 were preterm and 79 full-term (41 female, 71 male). The rate of seizures within the first 24 hours was higher following perinatal asphyxia (p=0.0001). Status epilepticus occurred in 26 patients (23.2%). Seizures were tonic in 21 patients (18.8%), subtle in 18 (16.1%), myoclonic in 15 (13.4%), and clonic in 15 (13.4%). EEG was normal or slightly abnormal in 69 patients (61.6%), and very abnormal in 16 (14.3%). Cranial imaging detected parenchymal hemorrhage in 22 cases (19.7%). Seizures responded to phenobarbital in 73 patients (65.2%). Etiologic factors included perinatal asphyxia in 22 cases (28.6%), intracranial bleeding in 19 (17%), metabolic disease in 12 (10.7%), unknown in 10 (8.9%), and miscellaneous. Prognosis was poorer in patients with perinatal asphyxia compared to those with metabolic disorders or unknown etiology. Epilepsy and global developmental delay, low Bayley cognitive and motor scores, and low language scores were more frequent following perinatal asphyxia compared to the group with metabolic disease or seizures of unknown etiology. Epilepsy developed in 35.7% patients, cerebral palsy in 27.6%, and global developmental delay in 50.8%. Prognostic factors in neurologic outcome included etiology, Apgar score, resuscitation at birth, abnormal EEG, neonatal status epilepticus, duration of AEDs, and response to acute treatment. (Yildiz EP, That B, Ekici B, et al. Evaluation of etiologic and prognostic factors in neonatal convulsions. **Pediatr Neurol** 2012 Sep;47(3):186-92). (Respond: Dr Ekici. E-mail: ekicibaris@yahoo.com).

COMMENT. Perinatal asphyxia is the most common cause of neonatal seizures and a risk factor for epilepsy, cerebral palsy and developmental delay. In one previous study of prognostic factors in 120 term infants with neonatal seizures, the prevalence of epilepsy, cerebral palsy and global developmental delay was 32%, 31%, and 43%, respectively. (Garfinkle J, Shevell MI. **Pediatr Neurol** 2011 Feb;44(2):88-96). It is unclear whether the cognitive impairment and developmental delay are in part the result of seizures or AED side effects. A small but significant depressant effect of long-term phenobarbital on cognitive function of children with febrile seizures is well known (Farwell JR et al. **N Engl J Med** 1990 Feb 8;322(6):364-9). Duration of AEDs was a prognostic risk factor in outcome in the present study. Further controlled studies of the long-term effects of AEDs on patients with neonatal seizures and epilepsy are required.

Status epilepticus and EEG abnormalities in the first year of life predict worse developmental outcome in children with Dravet syndrome also, complications that may be amenable to more specific therapy. (Brunklaus A et al. **Brain** 2012 Aug;135(Pt 8):2329-36). Dravet syndrome is a form of epilepsy associated with cognitive and motor disorders, resulting in encephalopathy. (Dravet C. **Brain** 2012 Aug;135(Pt 8):2309-11).

MOVEMENT DISORDERS

BRAIN GROWTH IN CHILDREN AT RISK FOR HUNTINGTON DISEASE

Researchers at the University of Iowa and Washington University, St Louis, MO, studied the effect of the mutant Huntington gene (mHTT) on measures of growth in children at risk for Huntington disease (HD). Measurements of growth (height, weight, body mass index [BMI], and head circumference) in 20 at risk gene-expanded children, aged 7-18 years, with no symptoms were compared with measurements in 14 gene-nonexpanded children and 138 age-matched healthy controls. Children with a CAG repeat length =/+ 39 were designated as gene-expanded. At risk gene-expanded children had significantly lower measures of head circumference, weight, and BMI. Head circumference was abnormally low even after correcting for height, suggesting a specific defect in brain growth, rather than a global growth abnormality. mHTT may play a role in atypical somatic, and particularly, brain development. (Lee JK, Mathews K, Schlaggar B, et al. Measures of growth in children at risk for Huntington disease. **Neurology** 2012 Aug 14;79(7):668-74). (Response: Jessica Lee. E-mail: jessica-k-lee@uiowa.edu).

COMMENT. Children tested as HD gene expanded were an estimated >3 decades from onset of the disease. Constant caloric burn due to chorea is a possible cause of weight loss in HD patients but not in preHD children. A primary abnormality in mitochondrial function and metabolic rate is more likely. (Damiano M, et al. Mitochondria in Huntington's disease. **Biochim Biophys Acta** 2010 Jan;1802(1):52-61 | Also cited by Lee JK).

LONG-TERM CLINICAL COURSE OF TOURETTE SYNDROME

Researchers at Catania University, and University Tor Vergata, Rome, Italy studied the course of Tourette syndrome (TS) after 10 years follow-up in 100 children. Of the "pure TS" group (n=38), 58% were unchanged, whereas 42% changed to TS+OCD phenotype. Of the "TS+ADHD" group (n=48), 62% changed to pure TS, 35% to TS+OCD, and 2% to TS+ADHD+OCD. Medication was required in 65%. Patients with comorbid condition at onset had a more severe prognosis and lower quality of life scores. (Rizzo R, Gulisano M, Cali PV, Curatolo P. **Brain Dev** 2012 Sep;34(8):667-73). (Respond: Dr Rizzo. E-mail: rerizzo@unict.it).

COMMENT. Patients with pure TS at onset have a favorable prognosis, whereas patients with TS and comorbid disorders, ADHD and OCD, are at risk of impaired quality of life. TS presents with a variety of clinical phenotypes that may change over time. Appropriate treatment of ADHD in children with TS may prevent behavioral problems in adulthood. Comorbidity with ADHD, occurring in 50% of TS patients, causes more disability than motor tics alone. (Spencer T et al. **Am Acad Child Adolesc Psychiatry** 1995 Sep;34(9):1133-9). Children with TS and ADHD have a 32% risk of learning disabilities. (Schuerholz LJ et al. **Neurology** 1996 Apr;46(4):958-65).