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

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CNS INFECTIONS

ADVANCES IN NEUROINFECTIOUS DISORDERS

Advances in therapy, outcome, and prediction of neurological infections published in the past year are reviewed from the University of Colorado Denver Health Sciences Center. Clinical trials of adjuvant dexamethasone therapy for bacterial meningitis result in a decrease in death rate and fewer unfavorable outcomes, but only in patients with meningitis caused by *Streptococcus pneumoniae.* Patients with meningitis and coexistent HIV infection are not benefited. Steroids should be reserved for immunocompetent patients with identified CSF gram-positive organism.

In patients with bacterial meningitis, prior antibiotic therapy may decrease the incidence of positive bacterial cultures in CSF and blood but does not decrease the frequency of positive CSF gram stains. Longer therapy is associated with higher CSF glucose and lower protein concentration but no change in CSF white blood cell count. CSF glucose and protein levels cannot be used to distinguish between bacterial and viral meningitis in patients who have received antibiotic pretreatment.

Recovery from neuroinvasive West Nile virus infection may be prolonged, but most patients return to normal functioning within 1 year.

Rapid RNA interference viral testing is successful in identifying novel pathogens in neuroinfectious diseases of unknown cause, leading to early treatment and potential new antiviral therapies. A lymphocytic choriomeningitis-like virus was identified as arenavirus in tissue, blood, and CSF specimens from three organ-transplant recipients who developed a fatal febrile encephalopathy 4-6 weeks after transplantation, when standard diagnostic techniques had failed. (Tyler KL. Neurological infections: advances in therapy, outcome, and prediction. **Lancet Neurol** Jan 2009;8:19-21). (Respond: E-mail: ken.tyler@uchsc.edu).

PEDIATRIC NEUROLOGY BRIEFS (ISSN 1043-3155) © 2009 covers selected articles from the world literature and is published monthly. Send subscription requests ($68 US; $72 Canada; $75 airmail outside N America) to **Pediatric Neurology Briefs - J. Gordon Millichap, M.D., F.R.C.P.- Editor,** P.O. Box 11391, Chicago, Illinois, 60611, USA. The editor is Pediatric Neurologist at Children's Memorial Hospital and Professor Emeritus, Northwestern University Medical School, Chicago, Illinois.

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COMMENT. Neuroinfectious disease is an expanding field of investigation, both in acute and in chronic disorders. The role of viral meningitis in the cause of epilepsy has received increasing attention (**Ped Neur Briefs** 2008;22:75). Maternal infection during pregnancy increases the risk of epilepsy in the offspring (**Ped Neur Briefs** 2008;22:45). Brain inflammation has a role in epileptogenesis (Choi J, Koh S. **Yonsei Med J** 2008;49:1-18).

CONTINUOUS EEG MONITORING IN CRITICALLY ILL PATIENTS WITH CNS INFECTIONS

The prevalence, predictors, and clinical significance of electrographic seizures (ESz) or periodic epileptiform discharges (PEDs) recorded during continuous electroencephalographic monitoring in critically ill patients with CNS infections were evaluated in a study at Columbia University Medical Center, New York, NY. Of 42 patients (mean age 39 years; range 0-82) identified between 1996 and 2007, 27 (64%) had viral infection, 8 (18%) bacterial, and 7 (17%) fungal or parasitic infections. Electrographic seizures were recorded in 14 (33%) patients and PEDs in 17 (40%). Either ESz or PEDs were recorded in 20 (48%) patients. Five (36%) of the 14 patients with ESz had clinical seizures. PEDs and viral infection were independently associated with ESz (P=0.001 and 0.02, respectively). ESz (P=0.02) and PEDs (P=0.01) were independently associated with poor outcome at discharge. Thirteen (31%) patients had severe disability, 3 were in coma or persistent vegetative state, and 5 died. (Carrera E, Claassen J, Oddo M, Emerson RG, Mayer SA, Hirsch LJ. Continuous electroencephalographic monitoring in critically ill patients with central nervous system infections. **Arch Neurol** Dec 2008;65:1612-1618).

COMMENT. Continuous EEG monitoring should be considered in patients with CNS infections and especially viral infection. Since electrographic seizures (ESz), recorded in 33% of the patients in this study, are associated with poor outcome, further studies are required to determine whether the ESz should be treated. The neurotropism and more extensive parenchymal damage after viral encephalitis compared to bacterial meningitis may explain the higher incidence of ESz with CNS viral infections.

NEUROMUSCULAR DISORDERS

BRACHIAL PLEXUS PALSY AND CORTICAL DYSPLASIA

Researchers at the Miami Children's Hospital report 2 infants with obstetrical brachial plexus palsy, ipsilateral leg weakness, and contralateral motor cortical dysplasia. Case 1, an 18-month-old girl presented for evaluation of a left brachial plexus palsy that followed a delivery complicated by shoulder dystocia. At 3 months, the left leg moved less and was shorter than the right. At 6 months, following a febrile seizure, a head CT revealed a smaller right hemisphere, and an EEG showed vertex spikes. Right-sided motor cortex dysplasia was diagnosed by MRI at 11 months of age and confirmed at 24 months. MRI of the brachial plexus and spinal cord were normal. At age 18 months, neurologic examination showed restricted left arm abduction and elbow flexion, decreased left biceps and

brachioradialis deep tendon reflexes, increased left patellar reflex, bilateral increase of Achilles tendon reflexes, left spontaneous Babinski, and shorter distance between the knee and ankle cutaneous creases on the left compared to the right leg.

Case 2, a 12-month-old boy with right brachial plexus palsy presented for evaluation of ipsilateral leg weakness, first noted by the mother when the infant attempted to walk. Neurological examination uncovered a tight right heel cord. Brain MRI revealed diffuse cortical dysplasia of the left hemisphere. (Alfonso I, Alfonso DT, Price AE, Grossman JAI. Cortical dysplasia and obstetrical brachial plexus palsy. **J Child Neurol** Dec 2008;23:1477-1480). (Respond: Israel Alfonso MD, Department of Neurology, Miami Children's Hospital, 3200 SW 60 Court, Suite 302, Miami, Fl 33155. E-mail: ialfonso@pediatricneuro.com).

COMMENT. The authors found no previous reports of an association of brachial plexus palsy and cortical dysplasia. They propose that this association helps explain the pathophysiology of brachial palsy in these patients by 2 mechanisms: prenatal shoulder girdle weakness and an abnormal arm position that increase the vulnerability of the plexus to stretch injury during delivery. Case 1 emphasizes the importance of attention to the length of the lower limbs and asymmetry in a neonatal neurological examination. MRI examination to exclude associated brain pathology should be considered in neonates with severe or complicated brachial plexus palsy.

Small Focal Cortical Dysplasia (FCD) lesions overlooked by routine MRI are visualized by high-resolution MRI, in a study at Montreal Neurological Institute, Canada (Besson P et al. **Brain** Dec 2008;131:3246-3255). Of 21 patients with small FCD, 17 (81%) were not identified initially, and 18 (86%) were located at the bottom of a sulcus. The knowledge that small FCD lesions are preferentially located at the bottom of an abnormally deep sulcus should aid the search for developmental cerebral lesions by routine MRI.

Outcome of Obstetric Brachial Plexus Injury correlates with force of downward traction of the fetal head in a study of 98 affected children at Goteborg University, Sweden (Mollberg M et al. **J Child Neurol** 2008;23:1424-1432). At 18 months follow-up, 82% had recovered completely and 18% had persistent functional neurological deficits.

DEMYELINATING DISEASES

RELAPSE RATE IN PEDIATRIC-ONSET MULTIPLE SCLEROSIS

Relapse rates were compared during 12 months or longer follow-up between 21 pediatric onset cases of multiple sclerosis (MS) seen at the Massachusetts General and 110 patients with adult-onset MS at the Brigham and Women's Hospitals, Boston, MA. Pediatric-onset patients had a 1.13 annualized relapse rate that was significantly higher than that in the adult-onset group (0.40) ($P<0.001$). The adjusted rate ratio was 2.81. The increased relapse rate in pediatric-onset MS remained highly significant when controlled for disease-modifying treatment time, and when age at onset was treated as a continuous variable. Pediatric-onset MS has a more inflammatory disease course than adult onset MS. (Gorman MP, Healy BC, Polgar-Turcsanyi M, Chitnis T. Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. **Arch Neurol** January 2009;66:54-59). (Respond: Tanuja

Chitnis MD, Partners Pediatric Multiple Sclerosis Center, Massachusetts General Hospital, ACC-708, 55 Fruit St, Boston, MA 02114. E-mail: tchitnis@partners.org).

COMMENT. Pediatric-onset MS has a slower rate of progression than adult-onset disease, according to several reports. The discrepancy between higher relapse rate and slower long-term progression of pediatric-onset MS is unexplained.

FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS TYPE 3 WITH DEMYELINATING CNS DISEASE

A case of familial hemophagocytic lymphohistiocytosis type 3 (FHLH3) presenting in a 3-year-old boy with fulminant demyelinating neurological disease is reported by researchers at Kravis Children's Hospital at Mount Sinai Medical Center, New York. Clinical examination 4 days after onset of neurological symptoms revealed an alert, active child with massive splenomegaly, and broad-based gait. MRI showed diffuse small demyelinating foci in subcortical and perivascular white matter. CSF protein was 55 mg/dL, and myelin basic protein was elevated (7.2 ng/mL, normal 0-4). EEG showed bilateral slowing. He had presented 6 weeks earlier at another hospital with irritability, abdominal pain, head tilt, neck and back pain, and inability to walk. Laboratory tests showed anemia, neutropenia and thrombocytopenia; serum ferritin was normal. Having recently returned from a trip to Honduras, he had received a course of amphotericin B for clinical suspicion of visceral leishmaniasis, later confirmed negative.

His neurological status deteriorated in hospital, with fever, progressive loss of head control, side-to-side head movements, right hemiparesis with tremor, and generalized hypotonia. MRI showed progressive demyelination. On suspicion of ADEM, he was treated with methylprednisolone without benefit. He developed seizures refractory to anticonvulsants. At 40 days after onset, typical diagnostic criteria for HLH were absent. Brain biopsy was consistent with ADEM. At 50 days after onset, soluble interleukin-2-receptor antibody levels were elevated, with increased expression of perforin-granzyme B. Sequence DNA analysis of blood showed a mutation in intron 10 of the Munc13-4 gene, diagnostic of FHLH3. The disease was too advanced for standard treatment with chemotherapy and stem cell transplantation; the patient continued to have seizures and died of sepsis 173 days after initial presentation. The family was offered genetic screening. (Weisfeld-Adams JD, Frank Y, Havalad V, et al. Diagnostic challenges in a child with familial hemophagocytic lymphohistiocytosis type 3 (FHLH3) presenting with fulminant neurological disease. **Childs Nerv Syst** February 2009;25:153-159). (Dr JD Weisfeld-Adams, Division of Medical Genetics, Mount Sinai School of Medicine, One Gustave L Levy Place, PO Box 1497, New York NY 10029. E-mail:james.weisfeld-adams@mssm.edu).

COMMENT. Familial HLH is an autosomal recessive multisystem disease characterized by fever, rash, splenomegaly, cytopenias, hyperferritinemia, and variable CNS manifestations with demyelination. This case report illustrates the difficulties encountered in diagnosis of HLH, and the need for a high index of suspicion and early molecular testing in cases of undiagnosed inflammatory CNS disease presenting as ADEM or pediatric MS. Leishmaniasis, considered as a possible cause of the symptoms in this case, shares similar features and is reported in 12% of HLH cases.

CONGENITAL CNS MALFORMATIONS

FETAL MRI IN PRENATAL DIAGNOSIS OF CNS ABNORMALITIES

The value of fetal MRI (fMRI) compared to ultrasound in the prenatal detection of CNS abnormalities and impact on counseling were determined in 25 pregnant women examined at University of Dusseldorf, Germany. Examination time was 27 to 51 minutes (41.8+/-6.1 min). Results were correlated with postnatal MRI, ultrasound and clinical follow-up. fMRI was performed 3-10 days after ultrasound between gestational week 22 and 34 (GW 26.1+/-3.6). Abnormalities suspected on fetal ultrasound were confirmed by fMRI in 8 cases. These included 2 cases of aqueductal stenosis hydrocephalus, and 1 each of hemimegalencephaly, microlissencephaly, ventriculomegaly, schizencephaly, brain tumor, and corpus callosum agenesis. Additional diagnoses or exclusions of suspected findings were established in 13 cases. The exclusions were corpus callosum agenesis in 4 cases and myelomeningocele, vermial aplasia, aqueductal stenosis, and Dandy-Walker malformation in 1 case each. Diagnoses were completely revised by fMRI in 4 cases. Postnatal MRI confirmed the fMRI findings in 11 patients. The quality of fMRI is technically comparable to postnatal MRI, and surgical treatment options are better defined than with ultrasound alone. (Messing-Junger AM, Rohrig A, Stressig R, Schaper J, Turowski B, Blondin D. Fetal MRI of the central nervous system: clinical relevance. **Childs Nerv Syst** February 2009;25:165-171). (Respond: AM Messing-Junger. E-mail: m.messing@Asklepios.com).

COMMENT. fMRI is superior to fetal ultrasound in detection of congenital CNS abnormalities. In institutions with trained professionals, fMRI is recommended in addition to ultrasound in patients with suspected pathologies that may require surgical interventions and parent counseling.

FUNCTIONAL MRI OF SENSORIMOTOR CORTEX IN PRETERM INFANTS

Functional MRI (fMRI) findings in a group of 5 pre-term infants were correlated with a unilateral passive forearm extension/flexion to relate the functional data to structural and behavioral data, in studies at the University of Bonn, Germany; and University Medical Center, Groningen, Netherlands. Measurement of blood oxygen level-dependent (BOLD) responses in the sensorimotor cortex showed bilateral activation during unilateral passive sensorimotor stimulation. The prevailing hemodynamic response was a negative blood oxygenation level-dependent signal. Positive blood oxygenation level-dependent response or failure to activate the sensorimotor cortex was found in patients with abnormal brain structural and behavioral problems. (Heep A, Scheef L, Jankowski J, et al. Functional magnetic resonance imaging of the sensorimotor system in preterm infants. **Pediatrics** January 2009;123:294-300). (Respond: Axel Heep MD. E-mail: axel.heep@ukb.uni-bonn.de).

COMMENT. The authors propose that their fMRI findings are compatible with a bilaterally distributed sensorimotor system in the preterm infant. The reductions of oxy/deoxy-Hb ratio in activated brain tissue may reflect ineffective neural processing during this maturational stage of rapid synapse formation. Positive blood oxygenation level-dependent responses or failure to activate the sensorimotor cortex in a preterm infant may predict abnormal cerebral development and need for careful follow-up. fMRI should provide a more effective measure of long-term developmental problems than the neonatal neurological exam.

CONGENITAL HYDROCEPHALUS RISK FACTORS

Risk factors associated with the pathogenesis of congenital hydrocephalus were evaluated in a 10 year retrospective study of 596 cases identified at the University of Mississippi Medical Center between 1998 and 2007. Significant risk factors included lack of prenatal care, multiparous gestation, maternal diabetes, maternal chronic hypertension, pregnancy-induced hypertension, and alcohol use during pregnancy. Hydrocephalus was familial in 12% cases. Except for an increased incidence of multiparous pregnancies and prenatal care in the first trimester in familial cases, no differences in risk factors were identified between sporadic and familial congenital hydrocephalus. The prevalence of familial cases within this cohort is much higher than that reported in X linked congenital hydrocephalus (2-7%), and suggests that the strong genetic factor in etiology is attributed to non-X linked patterns of inheritance. (Landingham MV, Nguyen TV, Roberts A, Parent AD, Zhang J. Risk factors of congenital hydrocephalus: a 10 year retrospective study. **J Neurol Neurosurg Psychiatry** February 2009;80:213-217). (Respond: Dr J Zhang, Department of Neurosurgery, University of Mississippi Medical Center, 2500 N State St, Jackson, MS 39216. E-mail: jhzhang@neurosurgery.umsmed.edu).

COMMENT. Both genetic and environmental factors are involved in the pathogenesis of congenital hydrocephalus. Some risk factors identified in this study should be susceptible to preventive measures, including improved prenatal care and nutrition, avoidance of alcohol, and prompt treatment of hypertension.

MODERATE PREMATURITY AND RISKS FOR CEREBRAL PALSY

The association between moderate prematurity and the incidence of adverse neurodevelopmental outcomes was assessed in a cohort of infants born in the Kaiser Permanente Medical Care Program of Northern California. Data covered 141,321 children born at >30 weeks gestation between Jan 1, 2000 and June 30, 2004, followed through Jan 30, 2005. Decreasing gestational age was associated with increased incidence of cerebral palsy (CP) and developmental delay (DD), even in those born at 34 to 36 weeks gestation. Late preterm infants were >3 times as likely to have CP as term infants. Children born at 34 to 36 weeks were marginally at higher risk of DD and mental retardation but not seizures. (Petrini JR, Dias T, McCormick MC, Massolo ML, Green NS, Escobar GJ. Increased risk of adverse neurological development for late preterm infants. **J Pediatr** February 2009;154:169-176). (Reprints: Joann R Petrini PhD MPH, March of Dimes National Office, 1275 Mamaroneck Ave, White Plains, NY 10605. E-mail: JPetrini@marchofdimes.com).

COMMENT. This study demonstrates an increased incidence of CP and DD/MR for children born moderately preterm. Late preterm infants should be examined neurologically and followed through early childhood to exclude or treat associated developmental learning disabilities. The risk of adverse neurodevelopmental delay or CP decreases with increasing gestational age.

MARKERS OF DEVELOPMENTAL SYNESTHESIA IN CHILDHOOD

The prevalence and development of grapheme-color synesthesia in children in the UK and US and its progression in longitudinal testing over 12 months (from ages 6/7 to 7/8) were studied at the Department of Psychology, University of Edinburgh, Scotland, UK. Individuals with synesthesia have the ability to merge sensory and/or cognitive functions. Everyday activities such as reading may trigger extraordinary experiences, eg colors or tastes. These atypical sensations arise spontaneously during development. In adults with synesthesia, a triggering stimulus (inducer) consistently triggers the same concurrent experience over time, referred to as the behavioral hallmark of synesthesia. Synesthetic experiences have anatomic and genetic roots. The average UK primary school has 2-3 grapheme-color synesthetes, and the average US primary school has 5. Synesthetic associations (eg. the letter "a"=carmine red) develop from chaotic pairings into a system of fixed cogno-sensory responses over time. Synesthesia has benefits and costs for the individual. Children who experience tastes from words read or spoken have difficulties in maintaining attention when reading, while grapheme-color synesthetes show superior color and digit memory. (Simner J, Harrold J, Creed H, Monro L, Foulkes L. Early detection of markers for synaesthesia in childhood populations. **Brain** Jan 2009;132:57-64). (Respond: Julia Simner, Department of Psychology, University of Edinburgh, 7 George Square, Edinburgh, EH8 9JZ, UK. E-mail: j.simner@ed.ac.uk).

COMMENT. In Webster, synesthesia is defined as a concomitant sensation, a subjective sensation or image of a sense (as of color) other than the one (as of sound) being stimulated. DeJong RN (**The Neurologic Examination**. 3rd ed, New York, Hoeber, 1967) uses the terms synesthesia, together with allachesthesia, allesthesia, and allochiria when the sensation of touch is experienced at a site remote from the point of stimulation. Neurologists have been aware of the phenomenon of synesthesia but, except for the neuropathologist, Yakovlev PI (**J Nerv Ment Dis** 1948;107:313-335), do not appear to acknowledge it as "an involuntary physical experience" that is real in the mind of the subject affected. Cytowic RE (**Psych** 1995;2(10) in a review of synesthesia describes the sensation as a cross-modal association, a familial trait, more common in females and non-right handed subjects. The neurological examination is usually normal. Synesthesia is considered a left hemisphere function, involving the hippocampus. Behavioral correlates include superior memory and weakened math and spatial perception. A recent resurgence in interest in synesthesia is lead by the field of neuropsychology and cognitive science. A PubMed search uncovers 7 references on synesthesia, none authored by a neurologist. Usually regarded as rare, two studies estimate that 5% of the population may experience at least one type of synesthesia. Epileptologists might be interested to research the prevalence of synesthesia in patients with temporal lobe seizures.

ANTICONVULSANT DRUGS

THROMBOPHILIC RISK FACTORS WITH VALPROIC ACID

Thrombophilic risk factors were investigated in 21 children (age range, 1-13 years) with epilepsy and recently treated with valproic acid monotherapy, in a study at Ankara University Medicine Faculty, Turkey. None had received any type of anticonvulsant previously. Thrombotic risk factors evaluated before and 9 to 12 months with treatment included homocysteine, lipoprotein(a), factor VIII, factor IX, protein C, protein S, antithrombin III, and activated protein C resistance levels. Thrombosis gene mutations (factor V Leiden and prothrombin) were also evaluated before treatment with valproic acid. Statistically significant elevation in lipoprotein(a) levels and reduction in fibrinogen levels were observed after therapy. Reduction in protein C and elevation in homocysteine levels were not significant. No thrombotic event occurred before or after treatment. Caution is advised in initiating valproic acid therapy in children with a history of stroke or thrombotic events. Routine investigation of thrombotic factors is not considered warranted. (Unal O, Deda G, Teber S, Ertem M, Akar N. Thrombophilic risk factors in epileptic children treated with valproic acid. **Pediatr Neurol** February 2009;40:102-106) (Respond: Dr Unal. E-mail: unalozlem@gmail.com).

COMMENT. Valproic acid therapy may increase lipoprotein(a) and decrease fibrinogen, leading to an increased risk of stroke or other thrombotic event. Before initiating valproic acid therapy for epilepsy, measurement of thrombophilic risk factors is warranted in patients with a history of stroke but not routinely,. Long-term treatment >12 months may warrant careful monitoring. The authors refer to a few reports of thrombophilia related to valproic acid, some precipitated by high altitude. In one report, protein C levels were reduced in 45% of 20 VPA-treated children and one suffered a stroke (Gruppo R et al. **J Pediatr** 2000;137:714-718).

VASCULAR DISORDERS

RISK FACTORS FOR INTRACRANIAL HEMORRHAGE

Risk factors for nontraumatic intracranial hemorrhage (ICH) in 85 children identified, 2000-2007, were studied retrospectively at Children's Hospital, Columbus, OH. Median age at presentation was 7 years (range, 7 days to 17 years), with 27 children 2 years or younger; 54 boys and 31 girls, sex ratio, 1.7:1. Location of hemorrhage was subarachnoid in 10, intraparenchymal in 61 (50 supratentorial, 11 infratentorial), and subdural in 14 children. Risk factors were intracranial vascular anomalies in 24 (AVM 11), congenital heart disease in 14, and brain tumor in 13. Infection was associated in 5 (6%) cases, and coagulation factor deficiencies in 4 (5%). Mortality was 34%, Of 48 survivors with follow-up information, 26 (54%) had no deficits; 22 had mild to severe deficits. (Wo WD, Lee J, Rusin J, Perkins E, Roach ES. Intracranial hemorrhage in children. **Arch Neurol** 2008;65:1629-1633).(Respond: WD Lo MD. E-mail:warren.lo@nationwidechildrens.org).