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

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CEREBRAL MALFORMATIONS

MIDBRAIN AND HINDBRAIN INVOLVEMENT IN LISSENCEPHALY

Involvement of the midbrain and hindbrain (MHB) in the various groups of lissencephalies was examined in an MRI study of 111 patients (aged 1 day to 32 years; mean 5 years 4 months) studied at University of California San Francisco, and centers in France, Belgium, and Turkey. The three major groups of lissencephaly (cLIS or LIS type 1; vLIS or variant LIS; and CBSC, cobblestone complex or LIS type 2) showed significant differences in the appearance and severity of associated MHB malformations; the least severe MHB malformations occurred with cLIS and the most severe with CBSC lissencephaly. The extent of cerebral lissencephaly was significantly correlated with the severity of MHB abnormalities (P= 0.0029). Based on the data obtained here and that in the literature, a new classification of lissencephalies is proposed: *Classic LIS* (LIS1, LIS1 mossaicism, DCX (XLIS); *Variant LIS* (ARX, RELN, VLDLR, ND1, ND2, ND3, TL-LIS; *Cobblestone complex* (FCMD-Fukuyama type, WWS, MEB; and related MD syndromes (CMD merosin deficiency). (Jissendi-Tchofo P, Kara S, Barkovich AJ. Midbrain-hindbrain involvement in lissencephalies. **Neurology** Feb 3, 2009;72:410-418). (Respond and reprints: Dr Patrice Jissendi-Tchofo, Radiology Department, Erasme Hospital, Route de Lennik 808, B-1070 Brussels, Belgium. E-mail: jisendi@gmail.com).

COMMENT. Lissencephaly or smooth brain is characterized by a paucity of gyri, ranging from complete agyria to localized pachygyria. It is usually classified in 2 groups, classic (cLIS or lissencephaly type 1), and cobblestone complex (CBSC, lissencephaly type 2). Five genes are identified as causing cLIS, and numerous genes are associated with CBSC, also called dystroglycanopathies. Most patients with CBSC have congenital muscular dystrophies with CNS involvement, including Fukuyama CMD, and Walker-Warburg

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syndrome. Relatively few investigators had stressed the importance of mesencephalic and rhrombencephalic involvement in association with cerebral cortical dysgenesis until the work of Sarnat, colleagues and others in the 1990s. A classification of cerebral malformations proposed by Sarnat et al in 2004 also stressed the inclusion of thalamic, brainstem and cerebellar malformations in association with lissencephaly and holoprosencephaly. In an editorial, Dr Sarnat reviews the progress of our understanding of the genetic programming of neural tube development and the need for research on a genetic mechanism for the association of forebrain and hindbrain malformations in the lissencephalies. (Sarnat HB. Cortical malformations. Looking behind the cortex. **Neurology** 2009;72:394-395).

SURGICAL OUTCOME IN FOCAL CORTICAL DYSPLASIA

The predictors of surgical outcome and relevance of pathological severity were determined in 166 consecutive patients with intractable epilepsy and focal cortical dysplasias treated surgically at Konkuk University Medical Center, and National University Hospital, Seoul, Korea. Poor surgical outcome was associated with incomplete resection of epileptogenic area, mild pathologic features, and secondary tonic-clonic seizures. Patients with severe pathologic features had MRI abnormalities. MRI findings, EEG, PET and ictal SPECT were not associated with surgical outcomes. (Kim DW, Lee SK, Chu K, et al. Predictors of surgical outcome and pathologic considerations in focal cortical dysplasia. **Neurology** Jan 20, 2009;72:211-216). (Respond and Reprints: Dr Sang Kun Lee, Department of Neurology, Seoul National University Hospital 28, Chongno Ku, Seoul ,110-744, Korea. E-mail: sangunlee@dreamwiz.com).

COMMENT. Patients with focal cortical dysplasia and intractable epilepsy are at risk of a poor surgical outcome, when associated with incomplete resection, mild pathologic features, or secondary tonic clonic seizures. Incomplete resection of focal cortical dysplasia was the main predictor of poor postsurgical outcome in 149 pediatric patients operated at the Miami Children's Hospital (Krsek P et al. **Neurology** 2009;72:217-223).

In practice, a negative MRI does not exclude a subtle cortical dysplasia that may underly refractory seizures. Newer imaging techniques may uncover small dysplasias amenable to treatment in specialized epilepsy and surgical centers. (Mathern GW. **Neurology** 2009;72:206-207).

VASCULAR DISORDERS

INTRACRANIAL ARTERIOPATHY AND ISCHEMIC STROKE

Repeated vascular imaging findings and clinical charts of 79 children with anterior circulation arterial ischemic stroke (AIS) and unilateral intracranial arteriopathy of the internal carotid bifurcation were studied at the University Medical Center, Utrecht, The Netherlands, and other centers in France, UK, and Canada. The characteristics of 5 (6%) patients with progressive and 74 (94%) with transient cerebral arteriopathy (TCA) were compared after a median follow-up of 1.4 years. Most infarcts were localized in the basal ganglia. Follow-up vascular imaging showed complete normalization in 23% of TCA

patients; 77% had residual arterial abnormalities, with improvement in 45% and stabilization in 32%. Before the arteriopathy stabilized or improved, transient worsening occurred in 14 (19%) of TCA patients; 13 (18%) had a recurrent stroke or TIA. Stroke was preceded by chickenpox in 44% of TCA patients and in none of those with progressive arteriopathies. Neurological outcome was good in 30 (41%) of the TCA patients and in none of the 5 with progressive arteriopathy. Progressive arteriopathy was associated with arterial occlusion, moyamoya disease and anterior cerebral artery involvement, and with stroke recurrence. (Braun KPJ, Bulder MMM, Chabrier S, et al. The course and outcome of unilateral intracranial arteriopathy in 79 children with ischemic stroke. **Brain** Feb 2009;132:544-557). (Respond: KPJ Braun MD, PhD, Department of Child Neurology, Rudolf Magnus Institute of Neuroscience, Wilhelmina Children's Hospital, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, the Netherlands. E-mail: k.braun@umcutrecht.nl).

COMMENT. In contrast to adults with stroke, the majority of childhood arterial ischemic strokes are caused by non-atherosclerotic arterial disease. Transient cerebral arteriopathy is a common cause and is characterized by infarction in the lateral lenticulostriate territory. The majority of patients in the above study had unilateral transient cerebral arteriopathy, and stroke was preceded by chickenpox (post-varicella arteriopathy) in 44%. Evidence supports a post-infectious inflammatory mechanism underlying transient cerebral arteriopathy.

CLASSIFICATION OF PERINATAL ISCHEMIC STROKE

Advances in classification, causes, treatment and outcome of perinatal ischemic stroke are reviewed by researchers at Alberta Children's Hospital, Calgary; and the Hospital for Sick Children, Toronto, Canada. Four perinatal stroke syndromes are described in order of decreasing incidence: 1) neonatal arterial ischemic stroke (accounts for two-thirds); 2) neonatal cerebral sinovenous thrombosis; 3) presumed perinatal ischemic stroke; and 4) periventricular venous infarction. MRI of the head and neck is the investigation of choice in perinatal stroke. Diffusion-weighted MRI provides information on timing for acute, focal infarction. MR angiography defines arterial occlusion or arteriopathy. MR venography defines location and extent of venous thrombosis, and diffusion weighted MRI confirms or excludes venous edema or infarction.

Maternal, prenatal, and placental risk factors include chorioamnionitis, prolonged rupture of membranes, preeclampsia, placental thrombi and intrauterine growth retardation. Intrapartum factors include neonatal encephalopathy with asphyxia that may co-occur with perinatal stroke. Prothrombotic and hematological factors occur in 20-68% of neonates with ischemic stroke. Cardiac evaluation is recommended in all cases of perinatal stroke, and complex congenital heart disease predisposes neonates to cerebral thromboembolism, especially during diagnostic and surgical procedures. Infection and inflammation are common in perinatal stroke, and the association with bacterial meningitis and chorioamnionitis requires further study.

Treatment involves maternal prevention approaches (counseling regarding smoking, weight control), rescue at risk brain tissue (anticoagulation, maintain normal blood sugar, temperature, oxygenation, blood pressure), and optimize outcome (study of hypothermia, treatment of seizures). Congenital hemiplegia and epilepsy are the most common

neurological deficits, and disorders of language, vision and cognition occur in 20-60% of perinatal stroke cases. Neuroimaging lesion size and location are helpful in prediction of outcome. Basal ganglia involvement correlates with poor prognosis. (Kirton A, deVeber G. Advances in perinatal ischemic stroke. **Pediatr Neurol** March 2009;40:205-214). (Respond: Dr Kirton, Division of Neurology, Alberta Children's Hospital, 2888 Shaganappi Trail NW, Calgary AB T3B 6A8, Canada. E-mail: adam.kirton@calgaryhealthregion.ca).

COMMENT. The distinction between specific causative factors and coincidental associations is a challenge, particularly with prenatal factors in the etiology of perinatal ischemic stroke. Advances in neuroimaging (functional MRI, diffusion tensor imaging, and transcranial magnetic stimulation) have improved prediction of outcome and should increase understanding of brain reorganization and plasticity.

Risk of epilepsy after perinatal stroke was studied by retrospective review of 64 children followed after 6 months of age at Indiana University School of Medicine (Garg BP et al. **J Pediatr** 2007;151:409-413; **Ped Neur Briefs** Oct 2007;21:79). Neonatal seizures were recorded in the NICU in 75% of cases. Epilepsy had developed in 67% between age 6 months and follow-up at a mean age of 43 months. Infarct on prenatal ultrasound and family history of seizures were significantly associated with development of epilepsy following perinatal stroke.

TRAUMATIC DISORDERS

SPINAL SUBDURAL HEMATOMA AND NON-ACCIDENTAL HEAD INJURY

The incidence of spinal pathology in 18 children with non-accidental head injury was determined in a study at Nottingham University Hospitals, UK. Between 2000 and 2007 children with non-accidental head injury had MRI of brain and whole spine; the spine was examined routinely in all suspected cases after 2005. Spinal subdural hematoma occurred in 8 (44%) cases. It was clinically occult in all cases, usually thoracic or lumbar in location, and large in 6. All had supratentorial and infratentorial intracranial subdural hematomas. Three of the 8 patients with supratentorial subdurals had skull fractures. Follow-up MRI of the spine within 1 to 3 months in 6 of the 8 cases showed reduction in size of the spinal subdural in 5 and complete resolution in 1. (Koumellis P, McConachie NS, Jaspan T. Spinal subdural hematomas in children with non-accidental head injury. **Arch Dis Child** March 2009;94:216-219). (Respond: Dr T Jaspan, Radiology Department, B Floor, Queen's Medical Centre, Derby Road, Nottingham NG7 2UH, UK. E-mail: tim.jaspan@nuh.nhs.uk).

COMMENT. A high incidence of occult spinal subdural hematoma is reported in children with non-accidental head injury and brain subdurals. Patients with suspected non-accidental head injury should receive MRI of brain and whole spine in all cases.

INFECTIOUS DISORDERS

SPINAL AND INTRACRANIAL EPIDURAL ABSCESS

Presentation, epidemiology, diagnosis and treatment of spinal epidural abscess (SEA) and intracranial epidural abscess (ICEA) are reviewed by researchers at The John's Hopkins University School of Medicine, Baltimore, MD, and Universidad de Santander, Columbia. Risk factors for SEA have increased in frequency and include injected-drug use, diabetes mellitus, invasive spinal procedures, spinal trauma, immunosuppression, skin infections, and bacteremia. The most common risk factor for ICEA is frontal sinusitis; 60-90% of cases are associated with otitis or sinusitis. Other factors include post-traumatic infections, nasal or mastoid surgical procedures, and congenital defects of the anterior cranial fossa. Gram-positive cocci, including Staphylococcus and Streptococcus are the most common causes of SEAs, with Staph aureus involved in 50-66% of cases. Mycobacterium tuberculosis is common in some geographic areas. Pseudomonas species are isolated from injected drug users with SEA. ICEAs are polymicrobial in origin, most commonly anaerobic gram-positive cocci, Staph and Strep spp (Strep anginosis) and gram-negative bacilli. CT and MRI are the preferred diagnostic tests. Medical and surgical treatments are reviewed in detail. Morbidity and mortality from SEA are high, especially in developing countries. Early diagnosis, specific microbiologic identification and prompt antimicrobial therapy can improve prognosis. In addition to broad-spectrum antibiotics, surgery is usually required in treatment of ICEAs. (Pradilla G, Hsu W, Rigamonti D, Pradilla Ardilla G. Epidural abscesses of the CNS. **Lancet Neurol** March 2009;8:292-300). (Respond: Daniele Rigamonti MD, The Johns Hopkins Hospital, Phipps Building, Room 104, 600 North Wolfe Street, Baltimore, MD 21287. E-mail: dr@jhmi.edu).

COMMENT. Prevalence of SEA although rare has increased, as a result of injected-drug users, while that of ICEA has decreased, following the introduction of more effective antimicrobial treatments. Prognosis is often poor due to delayed diagnosis. An awareness of the common risk factors leads to early recognition and prompt antimicrobial therapy. Most common causative factors are injected-drug use, immunosuppression and spinal surgical procedures in patients with SEA, and frontal sinusitis in ICEA.

SEIZURE DISORDERS

VISUAL FIELDS IN MOTHERS AND CHILDREN EXPOSED IN UTERO TO VIGABATRIN

Three mothers with 4 children exposed to vigabatrin in utero (but not breast fed) underwent perimetry and imaging of the retinal nerve fiber layer (RNFL) at the University Hospital of Wales and School of Optometry, Cardiff, UK. Two mothers showed vigabatrin-attributed visual loss and an abnormally attenuated RNFL. The third had an upper left quadrantanopia, consistent with previous temporal lobe surgery, and a normal RNFL. All four children, ages 6, 10, 15 and 18 years, had normal visual fields and RNFL thickness. Estimates of the in utero exposure to vigabatrin varied from 600 to 1410 mg/kg/day with a

mean of 1100. Children exposed pre-natally may be spared the visual toxicity of vigabatrin. (Lawthom C, Smith PEM, Wild JM. In utero exposure to vigabatrin: no indication of visual field loss. **Epilepsia** Feb 2009;50:318-321). (Respond: Dr John Wild, Cardiff School of Optometry and Vision Sciences, Cardiff University, Maindy Road, Cardiff CF24 4LU, Wales, UK. E-mail: wildjm@cardiff.ac.uk).

COMMENT. Vigabatrin-induced visual field loss manifests as a bilateral concentric constriction. It occurs in 30% of patients treated, and the incidence increases with duration and extent of exposure to the drug. Visual field perimetry examination is unsatisfactory under 9 years of age, but attenuation of the retinal nerve fiber layer thickness, estimated by optical coherence tomography, is a sensitive and specific test for vigabatrin toxicity.(Wild et al, 2006) Unlike the temporal quadrant atrophy seen in optic neuritis, vigabatrin toxicity is characterized by nasal quadrant constriction while the temporal quadrant is spared. Children exposed to vigabatrin by placental transfer only, in a dose 10 times that given to infants with infantile spasms, appear to be spared the visual field defect. Infants exposed after 6 months of age are 2.5 times more likely to show vigabatrin toxicity compared with those exposed before 6 months of age (Westall et al, 2007; cited by Lawthom et al).

Vigabatrin-induced visual field loss and age of exposure. Visual fields of 16 children treated with vigabatrin for infantile spasms were examined by Goldmann kinetic perimetry at age 6-12 years, in a study at Helsinki University Central Hospital, Finland (Gaily E et al. **Epilepsia** Feb 2009;50:206-216). Vigabatrin was started at a mean of 7.6 (range, 3.2-20.3) months. Mean duration of therapy was 21 months. Visual fields were normal in 15 children; a mild visual field loss occurred in one child who was treated with vigabatrin for 19 months. Children treated in infancy are less susceptible to vigabatrin-induced visual field loss than patients treated at a later age.

SEIZURE-INDUCED BRAIN DAMAGE IN THE NEONATE

The pathophysiology of neonatal seizures, and evidence for seizure-induced brain damage are reviewed by researchers from Montreal Children's Hospital, and Universite de Montreal, Quebec, Canada. Electrographically documented seizures with or without clinical manifestations are the most accurate concept of neonatal seizures. Incidence is 1.5-3.5 per 1000 live births, varying with risk factors such as low birth weight, prematurity, perinatal complications, and NICU availability. Etiology is the major determinant of outcome, but the seizure itself may be a factor. In animal models, neonatal seizures impair cognition, alter behavior, increase anxiety, and are associated with epileptogenesis. Clinically, the reported prevalence of epilepsy and abnormal neurodevelopment after neonatal seizures varies, ranging from 6.5% to 56% for epilepsy and from 19% to 67% for neurological abnormalities. Electrographic neonatal seizures, with or without clinical manifestations, correlate with increased morbidity and mortality. Risk factors for epilepsy include diffuse abnormalities on cranial imaging (more than focal), prolonged use of anticonvulsants, poor response of neonatal seizures to phenobarbital, abnormal EEG background, and acquired CNS infections. The efficacy of both phenobarbital and phenytoin in neonatal seizures is 50%, and no randomized controlled trial is reported to show improvement in neurodevelopmental outcome or prevention of epilepsy. Controlled trials of newer anticonvulsants and neuroprotective

agents are needed. (Thibeault-Eybalin M-P, Lortie A, Carmant L. Neonatal seizures: Do they damage the brain? **Pediatr Neurol** March 2009;40:175-180). (Respond: Dr Carmant, Epilepsy Clinic, Hospitalier Universitaire Sainte-Justine, 3175 Cote-Sainte-Catherine, Montreal, Quebec H3T 1C5, Canada. E-mail: lionel.carmant@umontreal.ca).

COMMENT. Although the experimental evidence from animal studies suggests that neonatal seizures can damage the developing brain, clinical reports are less convincing. Nonetheless, given the potential for seizure-induced brain damage, early and more effective treatment of neonatal seizures, including electrographic seizures, is generally advocated.

A study at Boston Children's Hospital on etiology and outcome of neonatal seizures found that global cerebral hypoxic-ischemia is the most frequent cause of neonatal seizures and a strong predictor of poor long-term outcome. (Tekgul H et al. **Pediatrics** 2006;117:1270-1280; **Ped Neur Briefs** April 2006;20:29-30). An abnormal neurologic examination in the neonatal period was an unreliable predictor of outcome.

Perilesional brain oedema and seizure activity: cause or effect? In response to a publication concerning seizures with calcified neurocysticercosis (Nash TE et al. **Lancet Neurol** 2008;7:1099-1105), Das A et al. question the proposed causative correlation of epileptogenesis and perilesional edema as an inflammatory response to calcified granulomas (**Lancet Neurol** 2009;8:225-226). Das et al agree that calcified lesions are seizure-causing foci but attribute the perilesional edema to the effect of the seizure per se. Reversible peri-ictal MRI abnormalities are known to develop immediately after a seizure and may resolve within a few days or weeks. Their precise pathogenesis is unknown.

Hippocampal swelling demonstrated by MRI within 48 hours of a prolonged febrile seizure is transitory and thought to be caused by vasogenic edema. The swelling resolves within 5 days and the shrinkage of the hippocampus that follows at 4-8 months is thought to represent a preexisting developmental hippocampal abnormality that predisposes to the prolonged FS (Scott RC et al. **Epilepsia** 2006;47:1493-1498). Alternatively, the hippocampal shrinkage is consistent with brain damage caused by the seizure with subsequent development of mesial temporal sclerosis and epilepsy. (See **Ped Neur Briefs** Oct 2006;20:77; and Nov 2003;17:83).

UTILITY OF AMPLITUDE-INTEGRATED EEG IN THE NICU

The problem of artifacts in using the amplitude-integrated electroencephalogram (AIE) to assess cortical function in premature infants in the NICU were studied at Weill Cornell Medical College, New York, NY. A pair of standard EEG electrodes were attached to scalp frontotemporal areas of 10 infants. Impedance was maintained at <10 kohms. Continuous AIE recordings were performed for at least 60 min repeatedly in the first month. Artifacts were identified as large amplitude difference between jagged wave peaks and troughs. When the AIE tracing spikes upward in amplitude, the accompanying raw EEG during these segments was classified as artifact. Of 1683 segments of 48 recordings analyzed, 31% were normal brain waves, 60% were artifacts, and 8% indeterminate. No clinical or electrographic seizures were noted. Artifact related to muscle activity and electrode placement detracts from the value of the AIE in assessing cortical function in

premature infants. (Suk D, Krauss AN, Engel M, Perlman JM. Amplitude-integrated electroencephalography in the NICU: frequent artifacts in premature infants may limit its utility as a monitoring device. **Pediatrics** Feb 2009;123:e328-e332). (Respond: Jeffrey M Perlman MB ChB, Weill Cornell Medical College, Department of Pediatrics, 525 E 68th St, Suite N-506, New York, NY 10065. E-mail: jmp2007@med.cornell.edu).

COMMENT. Amplitude-integrated EEG (aEEG) is a sensitive monitor of background cerebral activity in the early prediction of outcome after perinatal asphyxia in term infants. Abnormal aEEG is used in selection of patients for hypothermia. The above study introduces a note of caution in the use of the aEEG as an indicator of cortical function in premature infants in the NICU. The concurrent use of the conventional EEG and careful attention to electrode placement are suggested.

EVALUATION OF SLEEP DEPRIVATION IN THE PEDIATRIC EEG

The value of sleep deprivation to increase the yield of routine outpatient EEG in the diagnosis of epilepsy was assessed in a randomized, blinded comparison of routine EEG (REEG) versus sleep-deprived EEG (SDEEG) in 206 children aged 0 to 18 years referred by neurologists at Helen DeVos Children's Hospital, Grand Rapids, MI. Patients referred for EEG had >1 seizure (83%) or unclear spells (17%). Before the EEG, sleep-deprived patients averaged 4.9 hours sleep while those not sleep deprived had 7.9 hours sleep (P<.00001). Only 48% of the REEG group had adequate sleep for age vs 12% of the SD group (P<.0001). Of a total of 127 (64%) patients who fell asleep during the EEG, 73% of SDEEG group reached stage 2 sleep vs 55% of REEG group (P=.009). EEGs were normal in 67.7% of the REEG group vs 55.6% of SDEEG group (P=.08). Epileptiform discharges were recorded in 35% of REEG group vs 40% of SDEEG patients. No specific type of EEG abnormality was significantly more prevalent in the SDEEG group. Abnormal EEGs were more frequent in patients with clinically diagnosed seizures compared with those with unclear spells (P=.001). Odds of an abnormal EEG were also higher in the older (>3 years) age group vs younger children (P=.022). Sleep during the EEG did not influence the proportion of patients with epileptiform records in comparison with awake EEG only. Sleep deprivation, but not sleep during the EEG, provides a modest increase in EEG epileptiform discharges in children diagnosed with seizures by neurologists. Compared with a routine EEG, 11 SDEEGs would be required to identify 1 additional child with epileptiform discharges on EEG, (DeRoos ST, Chillag KL, Keeler M, Gilbert DL. Effects of sleep deprivation on the pediatric electroencephalogram. **Pediatrics** Feb 2009;123:703-708). (Respond: Steven T DeRoos MD, 1300 Michigan, Suite 102, Grand Rapids, MI 49503. E-mail: steven.deroos@devoschildrens.org).

COMMENT. Routine EEG fails to confirm a diagnosis of epilepsy in approximately 50% of patients with clinical seizures. Sleep and sleep deprivation are recommended to enhance the diagnostic yield. Despite the burden on parents and child of following the protocol of sleep deprivation (Nijhof SL et al, 2005), many authorities consider the benefits of sleep-deprived EEG (SD-EEG) to outweigh the inconvenience. Some studies that support the use of SD include Rowan AJ et al (1982), Klingler D (1982), and Leach JP et al (2006) who compared the yield of EEG abnormalities in 85 patients using 3 different protocols.