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

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AUTISM SPECTRUM DISORDER

MRI BIOMARKER FOR EARLY DIAGNOSIS OF AUTISM

In order to identify early risk markers for autism spectrum disorder (ASD), investigators at University of California Davis School of Medicine and Davis Children's Hospital conducted a longitudinal brain MRI study of infant siblings in conjunction with behavioral assessments leading to an outcome classification at 24 months or later (mean age 32.5 months). Fifty-five infants (33 'high-risk' infants having an older sibling with ASD and 22 'low-risk' infants having no relatives with ASD) were imaged at three time points: 6-9 months, 12-15 months, and 18-24 months of age. Compared to infants classified as developmental delay or typical development, 10 infants who developed ASD had significantly greater extra-axial fluid at 6-9 months, which remained elevated at 12-15 and 18-24 months. The amount of extra-axial fluid detected at 6 months was predictive of more severe ASD symptoms at time of outcome. Infants who developed ASD also had significantly larger total cerebral volumes at both 12-15 and 18-24 months of age. These novel findings raise the potential for use of structural MRI to aid in early detection (6-9 months of age) of children at risk for ASD. (Shen MD, Nordahl CW, Young GS, et al. Early brain enlargement and elevated extra-axial fluid in infants who develop autism spectrum disorder. **Brain** 2013 Sep;136(Pt 9):2825-35). (Respond: David G Amaral, The MIND Institute, University of California, Davis School of Medicine, Sacramento, CA 95817. E-mail: dgamaral@ucdavis.edu).

COMMENT. The clinical diagnosis of ASD is usually delayed until at least 18 months of age. This study provides a potential brain MRI biomarker for the earlier diagnosis and treatment of ASD in at risk infants.

Extra-axial fluid accumulation (communicating hydrocephalus) with rapid head growth in the first year of life typically resolves without intervention, but it may be associated with seizures and motor delays (Hellbusch LC. **J Neurosurg** 2007;107:119-

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125) and now is associated with development of ASD. Extra-axial fluid and rapid head growth in infancy is not always a benign reversible disorder.

Neurobiological abnormalities in infants who later develop ASD.

Studies since 2009 showing abnormalities in head circumference, electrophysiological markers and interhemispheric synchronization and differences in various brain regions (amygdala, cerebellum, frontal and temporal cortex) are reviewed by investigators at the University of Glasgow, Scotland. Cross-disciplinary approaches are essential to elucidate sequence of developmental abnormalities during early infancy leading to ASD (Allely CS, Gillberg C, Wilson P. **Behav Neurol** 2013 Aug 20. [Epub ahead of print]).

Eyeblink conditioning (EBC) is proposed as a non-invasive biomarker for ASD that can be employed shortly after birth (Reeb-Sutherland BC, Fox NA. **J Autism Dev Disord** 2013 Aug 14. [Epub ahead of print]). The neural circuitry for EBC involves sensory information from the cornea to the trigeminal nucleus, the interpositus nucleus and cerebellar cortex.

DEMYELINATING DISORDERS

CHANGES IN T-CELL HOMEOSTASIS IN MULTIPLE SCLEROSIS

Investigators at University Hospital, Heidelberg, and other centers in Germany, studied the composition of the peripheral T-cell compartment and regulatory T cell (Treg) function in 30 pediatric MS patients by multicolor flow cytometry and proliferation assays. Data from pediatric patients were compared to those obtained from 26 adult patients and 67 age-matched control donors. The proportions of both naïve and Treg cells are highest in the youngest children and decrease steadily with age. Pediatric MS patients had lower numbers of naive T cells, including recent thymic emigrants, whereas percentages of memory T cells were increased. Homeostatic changes in circulating T cells paralleled the pattern in adult MS. Treatment with immunomodulatory drugs attenuated the changes. Signs of early thymic involution are found in pediatric MS, suggesting that an intrinsic compromise in thymic-dependent T-cell neogenesis might contribute to MS pathogenesis. (Balint B, Haas J, Schwarz A, et al. T-cell homeostasis in pediatric multiple sclerosis. **Neurology** 2013 Aug 27;81(9):784-792).(Response: Prof Dr Wildemann. E-mail: Brigitte.wildemann@med.uni.heidelberg.de).

COMMENT. The authors conclude that the similarities in the T-cell compartment between adult and pediatric MS patients support a shared disease pathogenesis, immunologic disease mechanism, and response to therapy. Immunomodulatory drugs used in adult-onset MS might have the same effects in pediatric MS. Further studies are warranted to address whether premature senescence of the thymus and T-cell pool occurs at the earliest detectable stages of disease in children (Bar-Or A, Muraro PA. Premature immune senescence in children with MS: Too young to go steady. **Neurology** 2013 Aug 27;81(9):778-9).

PAROXYSMAL DISORDERS

MANAGEMENT OF REFLEX ANOXIC SEIZURES

Investigators at the Roald Dahl EEG Unit, Alder Hey Children's NHS Foundation, Liverpool, UK, review the definition, pathophysiology, clinical presentation, and management of reflex anoxic seizures (RAS) in children. Reflex asystolic syncope is proposed as the most appropriate alternative term; other terms for RAS include pallid breath-holding attacks and vasovagal syncope. A sudden injury or fright precipitates an acute loss of consciousness with opisthotonus, cyanosis, and clonic movements, resembling a short generalized tonic-clonic seizure. The underlying pathophysiology is a vagal-induced cardiac asystole with resultant cerebral hypoperfusion and consequent anoxia. EEG shows diffuse, high-amplitude slow wave activity during 10-15 sec of asystole, replaced by diffuse attenuated (low-amplitude) activity. After a further 5-20 sec, the vagal discharge stops, and the EEG shows a brief diffuse high-amplitude slow wave activity before returning to normal.

The differential diagnosis is an anoxic epileptic seizure, cyanotic breath-holding spell, or cardiogenic syncope. Anoxic epileptic seizures in which an initial anoxic seizure provokes a true epileptic seizure are very rare. Examples of cardiogenic syncope include prolonged QT syndromes (autosomal dominant Romano-Ward and autosomal recessive Jervell and Lange-Nielsen syndromes).

A careful history from an eyewitness of the onset of the attack is most important in diagnosis. Pharmacological treatment (e.g. atropine, scopolamine patch) may be helpful but carries a risk of adverse effects. Cardiac pacing is the only definitive treatment, reserved for frequent, most severe episodes. (Iyer A, Appleton R. Management of reflex anoxic seizures in children. **Arch Dis Child** 2013 Sep;98(9):714-7). (Response: Dr Richard Appleton. E-mail: Richard.appleton@alderhay.nhs.uk).

COMMENT. Reflex anoxic seizure (or reflex asystolic syncope) is important in the differential diagnosis of non-epileptic paroxysmal disorders in infants and pre-school-aged children.

Home video recordings of epileptic seizures induced by syncope are reported in 3 patients with "anoxic epileptic seizures." (Stephenson J, et al. **Epileptic Disord** 2004 Mar;6(1):15-9). These authors also reported a cohort of 9 children with syncope in which an initial anoxic seizure provoked a true epileptic seizure (Horrocks IA, Nechay A, Stephenson JBP, et al. **Arch Dis Child** 2005 Dec;90(12):1283-7). Contrary to these reports, the above author (Appleton R), a pediatric neurologist for over 22 years, avers he has never seen a child with epilepsy as a complication of RAS.

ELECTROCLINICAL SUBTYPES OF CINGULATE EPILEPSY

Investigators from the Cleveland Clinic, and University of Texas Southwestern Medical Center, studied consecutive cases of cingulate gyrus epilepsy identified retrospectively from their epilepsy databases from 1992 to 2009. Of 14 patients with

cingulate epilepsy confirmed by MRI and response to lesionectomy, 4 with lesions in the posterior cingulate location had electroclinical findings suggestive of a temporal origin of the epilepsy. Of 10 anterior cingulate cases, 6 in a typical (Bancaud) group had hypermotor/hyperkinetic seizures, rarely generalized, with fear, laughter, or severe interictal personality changes, and 4 were atypical, with simple motor seizures, frequently generalized, and a less favorable long-term surgical outcome. All atypical cases were associated with an underlying infiltrative astrocytoma. Posterior cingulate gyrus epilepsy is regarded as a pseudotemporal epilepsy. (Alkawadri R, So NK, Van Ness PC, Alexopoulos AV. Cingulate epilepsy: Report of 3 electroclinical subtypes with surgical outcomes. **JAMA Neurol** 2013 Aug 1;70(8):995-1002). (Response: Rafeed Alkawadri MD, Yale University School of Medicine, 15 York Street, LC17148, New Haven, CT 06510. E-mail: mhdrafeed.alkawadri@yale.edu).

COMMENT. Surface EEG is often inaccurate in localizing a deep-seated epileptogenic zone in a patient with cingulate epilepsy. Symptoms of cingulate epilepsy are heterogeneous and dependent on an anterior or posterior localization of the lesion. Anterior lesions are associated with hyperkinetic behavior, cycling and running and gelastic seizures, expressed by mirthless laughter. Posterior cingulate seizures resemble temporal lobe epilepsy. This report emphasizes the importance of an MRI-identifiable lesion in the diagnosis of cingulate epilepsy.

INTRACRANIAL PRESSURE DISORDERS

SPONTANEOUS INTRACRANIAL HYPOTENSION

Investigators at the Department of Neurosurgery, Cedars-Sinai Medical Center, Los Angeles, CA, evaluated 24 children (18 girls, 6 boys) with spontaneous intracranial hypotension, seen 2001-2012. Onset of symptoms was at mean age of 14.3 years (range, 2-19 years). The majority (23 patients) presented with orthostatic headaches, mainly occipital, and one with a non-positional headache. Additional symptoms included nausea, neck pain, dizziness, and hearing abnormalities. Precipitating headache factors included lifting, dance class, handstands, and football. Spinal MRI demonstrated a CSF leak in 12 (50%) patients, usually thoracic in location, and spinal meningeal diverticula without a leak in 10 (42%). Underlying connective tissue disorders in 13 patients (54%) included Marfan syndrome in 3, Marfan-like syndrome in 4, Ehlers-Danlos syndrome in 2, and hypomelanosis of Ito in 1. Dural ectasia with multiple meningeal diverticula were found in all 3 patients with Marfan syndrome.

Treatment consisted of bed rest and hydration, epidural blood patches in 23, with permanent resolution in 9 patients (39%). Injections of fibrin glue directed at the CSF leak were successful in 2 patients (25%). Surgical treatment had a good result in 10 patients (91%), with permanent resolution of symptoms. Acetazolamide for rebound high intracranial pressure headache was required in 5 patients. Overall, outcome was good in 22 patients (92%) and poor in 2 (8%). (Schievink WI, Maya MM, Louy C, Moser FG, Sloninsky L. Spontaneous intracranial hypotension in childhood and adolescence. **J Pediatr** 2013 Aug;163(2):504-10). (Response and reprints: Dr Wouter I Schievink. E-mail: SchievinkW@cshs.org).

COMMENT. **Intracranial hypotension and Marfan syndrome.** A PubMed search found several single case reports of spontaneous intracranial hypotension in children, two with Marfan syndrome. A 14-year-old girl followed for Marfan syndrome presented with a postural headache for a month, and MRI showed bilateral subdural hematomas. Large lumbosacral arachnoid diverticula were shown on spinal MRI. Headaches resolved after epidural blood patching. Dural ectasia is a common finding with Marfan syndrome. (Cheuret E, et al. **Childs Nerv Syst** 2008 Apr;24(4):509-13).

A 12-year-old girl with Marfan syndrome, sacral dural ectasia, and tonsillar herniation, presented with headache, unresponsive to surgical decompression of the foramen magnum. Further MR imaging demonstrated CSF leak at the level of the dural ectasia, and the headache resolved after blood patch of the leak. (Puget S, et al. **J Neurosurg** 2007 Jan;106(1 Suppl):48-52).

Skull thickening, paranasal sinus expansion, and sella turcica shrinkage are reported in a 29-year-old man with a history of VP shunt placement following traumatic brain injury at 9 years of age. MRI showed signs of chronic intracranial hypotension, and LP opening pressure was not recordable. Secondary installation of a valve to restore normal ICP is recommended. (Yoon MK, et al. **J Neurosurg Pediatr** 2013 Jun;11(6):667-72).

PSEUDOTUMOR CEREBRI SYNDROME

Investigators from the University of Texas Southwestern Medical Center, Dallas, and centers in Philadelphia and Salt Lake City, propose updated criteria for the diagnosis of pseudotumor cerebri (PTCS) and its variations. Idiopathic intracranial hypertension (IIH) is an appropriate term for a subset of patients with primary IH of unclear etiology, but not for those precipitated by an identifiable secondary cause. The syndrome is best described using the umbrella term PTCS. Required criteria for the diagnosis of PTCS are as follows: a) Papilledema, b) Normal neurologic examination (except cranial nerves), c) Normal MRI (or CT), d) Normal CSF composition, and e) Elevated lumbar puncture opening pressure (>250 mm for adults; >280 mm for children [250 if not sedated and not obese]).

With no papilledema, diagnosis requires (b) to (e) satisfied plus abducens nerve palsy.

Uncommon manifestations include a facial nerve palsy, hemifacial spasm, or radicular pain. CSF rhinorrhea or otorrhea and confirmation of a CSF leak are highly suggestive of PTCS diagnosis. Papilledema may be absent in recurrent PTCS cases because of gliosis in the nerve or optic atrophy.

Neuroimaging abnormalities highly suggestive of PTCS are: 1) Empty sella. 2) Flattening of posterior aspect of the globe, 3) Distension of the perioptic subarachnoid space, and 4) Transverse venous sinus stenosis. Tonsillar ectopia is more frequent in cases of PTCS but is not specific; it may be a sign of low CSF pressure, and may indicate an increased risk for herniation with LP. (Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. **Neurology** 2013 Sep 24;81(13):1159-65). (Response: Dr Friedman, E-mail: Deborah.Friedman@UTSouthwestern.edu).

COMMENT. Present diagnostic criteria and guidelines for the management of pediatric PTC do not consider pediatric aspects, according to a study involving all pediatric hospitals in Germany (Tibussek D, et al. **Klin Padiatr** 2013 Mar;225(2):81-5). The annual incidence was 0.5 per 100,000 children. A wide range of vision problems included papilledema, visual loss, diplopia, visual field defect, disturbed color and stereo vision. Papilledema was absent in 10 (16.4%) of a total of 61 patients treated Jan to Dec 2008. The importance of the ophthalmological exam was emphasized.

In a study of 42 patients with average age at onset of 10.8 years (range, 12 months to 17 years), obesity was found in 11 (26%). Headache occurred in 76%. Various etiologic factors were associated, including trauma in 2, hypervitaminosis A, corticosteroid withdrawal, oral contraceptives, Guillain-Barre syndrome, urinary tract infection, varicella-zoster virus infection, and dural venous sinus thrombosis associated with otitis media. Prompt diagnosis and medical treatment are important to avoid visual loss. (Per H, et al. **Brain Dev** 2013 Jun;35(6):561-8).

An unusual case of a 13-year-old boy presented with acute paresis of the left abducens, facial and vagus nerves. Brain MRI and angiography were normal. LP revealed an intracranial pressure of 575mmH2O. Treatment with acetazolamide resulted in improvement with no sequelae (Antoun J et al. **J Fr Ophthalmol** 2013 May 31 [Epub ahead of print]).

DEVELOPMENTAL MALFORMATIONS

WILLIAMS-BEUREN SYNDROME WITH BRAIN DYSPLASIA

Investigators from Jichi and Yokohama City Universities, Japan, report a patient with the common Williams-Beuren syndrome (WBS) deletion in 7q11.23 who presented with severe cerebral and cerebellar dysplasia and progressive hypertrophic cardiomyopathy. Facial characteristics included downward slanting of the palpebral fissure, blepharophimosis, strabismus, right iris hypopigmentation, low-set ears, high-arched palate, broad nose, thick lips, wide mouth, and micrognathia. Associated abnormalities included a deep, husky voice, hearing impairment by brainstem auditory responses, hypoplastic toes with nail aplasia, and contractures of hip and knee joints. Progressive hypertrophic cardiomyopathy manifested with ventricular septal defect at birth, right ventricular hypertrophy at 1 month, and left ventricular hypertrophy and mitral valve insufficiency at age 2 months. Supravalvular aortic stenosis commonly found with WB syndrome was absent.

Brain MRI showed congenital hydrocephalus, hypoplasia of the cerebellum and brain stem, and agenesis of the corpus callosum. At 3 months of age, he developed recurrent generalized tonic convulsions daily. Laboratory findings included mild hypocalcemia, low blood sugar, and low free T4 and high TSH consistent with hypothyroidism. The patient died with heart failure at age 1 year 5 months. (Okamoto N, Yamagata T, Yada Y, et al. Williams-Beuren syndrome with brain malformation and hypertrophic cardiomyopathy. **Brain Dev** 2013 Jul 27 [Epub ahead of print]). (Response: Dr Takanori Yamagata, Department of Pediatrics, Jichi Medical University, Tochigi, Japan. E-mail: takanori@jichi.ac.jp).

COMMENT. The original reports of Williams (alt. Williams-Beuren) syndrome appeared in the journal Circulation, 1961 and 1962, with emphasis on "Supravalvular aortic stenosis." Diagnosis of Williams syndrome involves recognition of physical features and markers, followed by a confirmatory genetic test. This case report is presented as the first patient with WB syndrome to have a congenital CNS anomaly in addition to progressive hypertrophic cardiomyopathy. Neurologic symptoms previously reported include mild microcephaly, intellectual disability, and personality disorders (hyperverbal). Abnormalities in the cerebellum, right parietal cortex, and left frontal cortex are consistent with visual-spatial difficulties. Increased volume of the left auditory cortex correlates with a rhythm propensity and fondness of music. Neuropsychological, neurological, and neuroanatomical profile of Williams syndrome is compared to that of Down syndrome (Bellugi U et al. **Am J Med Genet** 1990;37(Suppl. S6):115-25). For a clinical guide to symptoms and diagnosis of Williams and other syndromes, see Millichap JG. **Neurological Syndromes.** New York: Springer; 2013. 279 p.

JOUBERT SYNDROME, A CILIOPATHY

Investigators at Neurogenetics Unit, Mendel Laboratory, Rome, and University of Salerno, Italy, review the clinical features and genetic basis of Joubert syndrome, overlap with other ciliopathies, and the multifaceted roles of primary cilia in CNS development. Joubert M. and colleagues first described a familial agenesis of the cerebellum, manifested by episodic hyperpnea, abnormal eye movements, ataxia and retardation (**Neurology** 1969 Sep;19(9):813-25). The characteristic malformation involving the cerebellum and brainstem, the MRI hallmark of the syndrome, is called the "molar tooth sign." Associated CNS defects include ventriculomegaly, meningo-encephalocele, polymicrogyria, periventricular nodular heterotopia, hypothalamic hamartoma, and corpus callosum defects. Specific Joubert syndrome subgroups are correlated with different causative genes, one known by the acronym COACH (cerebellar vermis hypoplasia, oligophrenia, ataxia, coloboma, and hepatic fibrosis). A total of 21 causative genes have been identified, all encoding for proteins of the primary cilium that has a key role in development. An increasing number of heterogeneous disorders are being causally related to mutations in ciliary genes. (Romani M, Micalizzi A, Valente EM. Joubert syndrome: congenital cerebellar ataxia with the molar tooth. **Lancet Neurol** 2013 Sep;12(9):894-905). (Response: Prof Enza Maria Valente: E-mail. e.valente@css-mendel.it).

COMMENT. Prenatal abnormal features of the fourth ventricle in fetuses with Joubert syndrome and related disorders are reported in 7 subjects, all showing the molar tooth sign using ultrasound and/or MRI. (Quarello E et al. **Ultrasound Obstet Gynecol** 2013 Jul 19 [Epub ahead of print]). The term "Joubert syndrome" now encompasses all molar tooth sign-related disorders, and the term "Joubert syndrome and related disorders" is no longer in favor. Variable clinical manifestations associated with the molar tooth sign are not distinct syndromes, but part of a wide phenotypic range characteristic of Joubert syndrome.

ENCEPHALITIS

IMMUNOMODULATORY THERAPY FOR RASMUSSEN SYNDROME

Investigators from the National Epilepsy Center, Shizuoka, Gifu University, Tokyo Women's Medical University, National Center of Neurology and Psychiatry, and Okayama University School of Medicine, Japan, examined seizure, cognitive, and motor outcomes in 49 patients referred with Rasmussen encephalitis (RS) and recently had received initial immunomodulatory therapy: regular IV immunoglobulin (IVIg) at a dose of 100 mg/kg/day, methylprednisolone steroid pulse therapy at a dose of 30 mg/kg/day (children) for 3 days, and tacrolimus 0.1 mg/kg/day. Mean age at onset was 8.7 +/-10.5 years. Seizure-free rate was 71% after functional hemispherectomy (FH), seizure response rate was 81% for regular steroid pulse therapy, 42% for tacrolimus therapy, and 23% for regular IVIg therapy. IQ higher than 80 was attained by 50% of patients treated with steroid pulse therapy, in 43% following IVIg therapy, in 29% after tacrolimus therapy, and 0% in patients treated surgically by FH. In patients without MRI lesions compared to those with advanced lesions, percent of patients with IQ>80 were 100% cf. 37%. Motor paresis was improved only in immunomodulatory treated patients. Motor function was aggravated in 100% patients treated by FH, 62% by regular IVIg, and 10% by regular steroid pulse therapy. (Takahashi Y, Yamazaki E, Mine J, et al. Immunomodulatory therapy versus surgery for Rasmussen syndrome in early childhood. **Brain Dev** 2013 Sep;35(8):778-85). (Response: Dr Y Takahashi, National Epilepsy Center, Shizuoka, Japan. E-mail: takahashi-ped@umin.ac.jp).

COMMENT. The authors conclude that early initiation of regular steroid pulse therapy is the recommended first-line immunomodulatory therapy in patients with suspect RS. Regular pulse therapy yields superior seizure outcome and better cognitive outcome in early stage RS, before the appearance of MRI lesions. Functional hemispherectomy may be indicated in patients with neurological deficits equivalent to those that would result from surgery, mainly in patients with disease involving the non-dominant hemisphere.

Diagnostic criteria for Rasmussen encephalitis. Investigators at Boston Children's Hospital studied the sensitivity, specificity, and positive and negative predictive values of the Bien diagnostic criteria for RE, using pathology findings for diagnosis (Olson HE, et al. **Epilepsia** 2013 Aug 23 [Epub ahead of print]). In 82 patients evaluated for RE, the Bien criteria had a sensitivity of 81%, with 4 false negatives and 5 false positives.

The Bien diagnostic criteria are met if either all 3 criteria of Part A or two of 3 criteria of Part B are present. Part A criteria are clinical (focal seizures, with or without epilepsia partialis continua), EEG (unihemispheric slowing with or without epileptiform activity), and MRI (unihemispheric focal cortical atrophy). Part B criteria are clinical (epilepsia partialis continua), MRI (progressive unihemispheric focal cortical atrophy) and histopathology (T cell dominated encephalitis and reactive astrogliosis). (Bien CG, et al. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement. **Brain** 2005 Mar;128(Pt 3):454-71).