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

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ANTIEPILEPTIC DRUGS

PRENATAL VALPROATE AND RISK OF AUTISM

Investigators at Aarhus University Hospital, Denmark; and Centers for Disease Control, Atlanta, GA, conducted a population-based study of all children born alive in Denmark from 1996 to 2006 to determine the risk of autism spectrum disorders (ASD) and childhood autism (CA) in children exposed to valproate during pregnancy. [ASD includes CA, Asperger syndrome, atypical autism, and pervasive developmental disorders]. The Danish Psychiatric Central Register was used to identify children diagnosed for the first time with ASD and with CA. The National Hospital Register was used to identify children diagnosed with congenital malformations and parents diagnosed with epilepsy. Of 655,615 children born from 1996-2006, 5437 were identified with ASD, including 2067 with CA. The mean age of the children at end of follow-up was 8.84 years (range 4-14 years). The estimated absolute risk of ASD after 14 years of follow-up was 1.53% for ASD and 0.48% for CA. In the overall cohort, the 508 children exposed to valproate had an absolute risk of 4.42% for ASD and 2.50% for CA. In the 6584 children born to women with epilepsy, the absolute risk of ASD among 432 children exposed to valproate was 4.15%, and the risk of CA was 2.95%. In comparison, the risk among 6152 children not exposed to valproate was 2.44% for ASD and 1.02% for CA. (Christensen J, Gronborg TK, Sorensen MJ, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. **JAMA** 2013 Apr 24;309(16):1696-703). (Response: Jacob Christensen PhD, Department of Neurology, Aarhus University Hospital, E-mail: Jakob@farm.au.dk).

COMMENT. Maternal exposure to valproate during pregnancy is associated with a small (<5%) but significantly increased risk of autism spectrum disorder and childhood autism in the offspring, even after adjusting for effects of parental epilepsy and

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psychiatric disease. The risk of childhood autism following valproate use in women with epilepsy is lower compared with the overall risk. Exposures to carbamazepine, oxcarbazepine, lamotrigine and clonazepam monotherapy are not associated with increased risks of ASD and CA. The possible protective effects of folic acid ingestion during pregnancy are not evaluated. (Suren P, et al. **JAMA** 2013 Feb 13;309(6):570-7) (Schmidt RJ, et al. **Am J Clin Nutr** 2012 Jul;96(1):80-9).

The risks of valproate in women of childbearing potential (15-44 years) may outweigh the benefits. Given the evidence linking fetal valproate exposure to congenital malformations, cognitive impairments (**Pediatr Neurol Briefs** 2013 Apr;27(4):31), and autism, the use of valproate in potentially parous women should be minimized, restricted to cases with no available alternative treatment, and only introduced (in low dosage) after potential risks are fully explained. (Meador KJ, Loring DW. Editorial. Risks of in utero exposure to valproate. **JAMA** 2013 Apr 24;309(16):1730-1).

Fetal Growth and Risk of Autism. Investigators at the University of Manchester, UK, and other centers studied the relationship between fetal growth and autistic spectrum disorder (ASD). Deviance in fetal growth at either extreme and preterm birth are strong independent risk factors for later ASD, especially with intellectual disabilities. Genetic and environmental factors might influence fetal growth and predispose to ASD. (Abel KM, et al. Deviance in fetal growth and risk of autistic spectrum disorder. **Am J Psychiatry** 2013 Apr 1;170(4):391-8).

ANTIEPILEPTIC DRUG DISPOSITION IN PREGNANCY

Investigators at the Karolinska Institute, Stockholm, Sweden; and centers in Oslo, Norway, and Milan, Italy, reviewed the literature on gestational effects on pharmacokinetics of older and newer antiepileptic drugs (AEDs). Absorption, distribution, metabolism, and elimination may be affected depending on the type of AED. A pronounced decline in serum concentrations is seen for AEDs eliminated by glucuronidation (UGT), especially lamotrigine. Serum levels of AEDs cleared mainly through the kidneys, e.g. levetiracetam, decline significantly. In contrast, carbamazepine is affected only marginally by pregnancy. Data on newer drugs are either lacking or vary widely: pregabalin, lacosamide, retigabine, and eslicarbazepine acetate. In general, declining serum concentrations in pregnancy are associated with deterioration in seizure control. AED serum monitoring and dose adjustment based on falling levels may be important, particularly when a patient's levels are titrated to the lowest effective AED dose and serum concentration before pregnancy. (Tomson T, Landmark CJ, Battino D. Antiepileptic drug treatment in pregnancy: Changes in drug disposition and their clinical implications. **Epilepsia** 2013 Mar;54(3):405-14). (Response: Torbjorn Tomson, Department of Neurology, Karolinska University Hospital, Stockholm, Sweden. E-mail: trobjorn.tomson@karolinska.se).

COMMENT. Pharmacokinetic changes during pregnancy are rapid and labile and have a profound effect on the management of epilepsy. The risks of uncontrolled seizures are weighed against potential teratogenic effects of AEDs.

LOCALIZATION OF GENERALIZED SPIKE AND WAVE DISCHARGE AND VALPROATE RESPONSE

Investigators at Universities of Cincinnati, OH, and Birmingham, Alabama; and Montreal Neurological Institute, Canada, studied the EEG and functional magnetic resonance imaging (fMRI) in 89 patients with idiopathic generalized epilepsy (IGE), (25 with generalized spike and wave discharges (GSWD) identified in EEG), and compared patients with valproate (VPA)-refractory and VPA-responsive IGE. The fMRI blood oxygen-level dependent (BOLD) correlates of GSWD in the entire group of patients involved midline thalamus, frontal regions and temporal lobes. A comparison of VPA-responsive and VPA-resistant patients showed BOLD signal increases in the VPA-resistant patients in medial frontal cortex, along the paracingulate gyrus and anterior insula bilaterally. VPA-resistant and VPA-responsive patients have different GSWD generators that may explain the reason for different responses and resistance to VPA in some cases. (Szaflarski JP, Kay B, Gotman J, Privitera MD, Holland SK. The relationship between the localization of the generalized spike and wave discharge generators and the response to valproate. **Epilepsia** 2013 Mar;54(3):471-80). (Response: Jerry P Szaflarski, Department of Neurology, UAB Epilepsy Center University of Alabama at Birmingham, AL 35294. E-mail: szaflaj@uab.edu).

COMMENT. The combining of EEG and fMRI is a noninvasive method of investigation of brain regions involved at the time of epileptic discharges (Gotman J, Pittau F. **Epilepsia** 2011 Jul;52 Suppl 4:38-42). Neuronal discharges during an interictal spike or spike-wave burst result in increased metabolism and blood flow, reflected in the blood oxygen-level dependent (BOLD) signal measured by fMRI. EEG-fMRI helps localize epileptic foci in nonlesional frontal lobe epilepsy; it also demonstrates thalamic involvement in generalized epileptic discharges.

UPDATED ILAE REVIEW OF ANTIEPILEPTIC DRUG EFFICACY

The International League Against Epilepsy (ILAE) Subcommission on AED Guidelines reviewed the literature from July 2005 to March 2012 and combined results with previous analysis (2006) to provide a comprehensive update of level of AED efficacy as initial monotherapy with newly diagnosed or untreated epilepsy. Class of study (I, II, and III) and level of efficacy (A, B, C, and D) are recorded. The combined analysis (1940-2012) includes a total of 64 randomized controlled trials (RCTs) [7 with class I evidence, 2 with class II], and 11 meta-analyses.

In children with partial-onset seizures, 2 RCTs were class III because of an open-label design, too short treatment duration, and a forced exit criteria, and 4 new meta-analyses included OXC versus PHT, LTG versus CBZ, and CBZ versus OXC. CBZ is most frequently studied (n=12) followed by VPA (n=7) and PHT (n=6). OXC is the only adequate comparator for childhood partial-onset seizures and is established (level A); CBZ, PB, PHT, TPM, VPA, and VGB are possibly (level C); and clobazam (CLB), CZP, LTG, and ZNS are potentially (level D) efficacious/effective as initial monotherapy.

In children with generalized-onset tonic-clonic seizures, CBZ, PB, PHT, TPM, and VPA are possibly (level C) and OXC is potentially (level D) efficacious/effective,

but there are no adequate comparators. CBZ and PHT may precipitate or aggravate generalized-onset tonic-clonic seizures (class IV suggestive evidence).

In children with absence seizures, 3 AEDs (VPA, ESM, and LTG) had new class I or class II evidence of efficacy; LEV had additional class III evidence of efficacy. ESM and VPA are adequate comparators and are established (level A); LTG is possibly (level C) effective. GBP is established as ineffective (level F); AEDs that may precipitate or aggravate absence seizures (class IV scattered reports) include CBZ, OXC, PB, PHT, TGB, and VGB. LEV failed class III placebo-controlled trial and efficacy is undetermined.

In children with BECTS, CBZ and VPA are possibly (level C) and GBP, LEV, OXC, and STM are potentially (level D) effective. For *juvenile myoclonic epilepsy,* TPM and VPA are potentially (level D) effective; CBZ, GBP, OXC, PHT, TGB, and VGB may precipitate or aggravate absence, myoclonic, and sometimes, generalized tonic-clonic seizures. LTG exacerbated seizures in JME (level F) in one report. (Glauser T, Ben-Menachem E, Bourgeois B, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. **Epilepsia** 2013 Mar;54(3):551-63). (Response: Tracy A Glauser, Comprehensive Epilepsy Center, Division of Neurology, Cincinnati Children's Hospital, OH 45229. E-mail: tracy.glauser@cchmc.org).

COMMENT. The authors stress that their report is a working framework and not a mandatory rulebook. Multicenter studies and trial designs are needed to determine the efficacy of new AEDs compared to the old, but the most appropriate AED for a specific patient is decided by the judgment and expertise of the individual physician. Management of epilepsy remains partly an art as much as a science, especially when polytherapy is involved and overused.

ENCEPHALOPATHIES

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

Investigators at University of Milan, Italy, report a 6-year-old boy who presented with left-sided weakness followed by status epilepticus, left-sided tonic-clonic seizures with secondary generalization, without fever. The seizure was preceded by an acute gastroenteritis in the week prior to admission. His blood pressure was 139-112 mm/Hg (>95th percentile). Control of status by iv phenobarbital was accompanied by resolution of hypertension. Neurological examination revealed hypotonia and hyporeflexia of the left side. Blood and CSF examinations were normal, including PCR for Enterovirus. MRI showed bilateral asymmetric low intensities in the white and gray matter of posterior parietal and occipital lobes, affecting the right hemisphere predominantly. EEG showed an encephalopathic pattern in posterior regions with no epileptiform discharges. The patient recovered completely within the following 6 days, and follow-up exams in 3 and 12 months were normal, including neurological, EEG, MRI, and blood pressure, and with no recurrence of seizures. (Mameli C, Dilillo D, Spiri D, Cerini C, Fasan S, Zuccotti GV. Status epilepticus as manifestation of posterior reversible encephalopathy syndrome in a healthy child. **Pediatr Neurol** 2013 May;48(5):418-20). (Response: Dr Mameli,

Department of Pediatrics, L Sacco Hospital, University of Milan, 20157 Milano, Italy. E-mail: mameli.chiara@hsacco.it).

COMMENT. Posterior reversible encephalopathy syndrome (PRES), first described in 1996 (Hinchey J, et al. **N Engl J Med** 1996 Feb 22;334(8):494-500), is characterized clinically by headache, altered awareness, visual disturbance, and seizures, and radiologically by transient posterior lesions in subcortical white matter. PRES is associated with a rapid rise in blood pressure that may underlie the encephalopathy. The pathophysiology of PRES is not completely understood, but predisposing conditions include renal and hemato-oncologic diseases and use of chemotherapeutic immunosuppressive drugs. (Siebert E, et al. **Eur J Paediatr Neurol** 2013 Mar;17(2):169-75 [Cited by Mameli]). Other conditions reported in association with PRES are organ and bone marrow transplantation, autoimmune disease, Guillain-Barre syndrome, sickle cell anemia, hemolytic-uremic syndrome, and iv immunoglobulin administration.

SLC19A3 EARLY-INFANTILE, LETHAL ENCEPHALOPATHY

Investigators from VU Medical Centre, Amsterdam, The Netherlands, identified seven patients with severe encephalopathy who shared a previously undescribed MRI pattern with cystic degeneration of the white matter and progressive cerebral, cerebellar and brainstem atrophy. All patients showed rapid deterioration of brain function soon after birth, followed by respiratory failure and death. Whole-exome sequencing revealed pathogenic, heterozygous missense mutations in the SLC19A3 gene, encoding the second thiamine transporter. Pathology of brain tissue demonstrates cerebral atrophy and lesions similar to Leigh's syndrome. This new, severe, lethal phenotype broadens the phenotypic spectrum of SLC19A3 mutations and is recognized by the associated MRI pattern of brain degeneration. (Kevelam SH, Bugiani M, Salomons GS, et al. Exome sequencing reveals mutated SLC19A3 in patients with an early-infantile, lethal encephalopathy. **Brain** 2013 May;136(Pt 5):1534-43). (Response: Marjo S van der Knaap, Department of Child Neurology, VU Medical Centre, de Boelelaan 1117, 1081 HV Amsterdam, The Netherlands. E-mail: ms.vanderknaap@vumc.nl).

COMMENT. MRI pattern of initial swelling with T-hyperintensities followed by rapid degeneration and brain atrophy allows early diagnosis of a rapidly progressive infantile encephalopathy caused by SLC19A3 mutations.

MIGRATING PARTIAL SEIZURES OF INFANCY

A national surveillance study in conjunction with the British Paediatric Neurology Unit was undertaken to further define the clinical, pathological and molecular genetic features of migrating partial seizures of infancy (MPSI), a rare early infantile epileptic encephalopathy with poor prognosis. In 14 patients reported during the 2 year study period, MPSI was associated with an expanded spectrum of clinical features including gut dysmotility and movement disorder, EEG features including hypsarrhythmia with infantile spasms and burst suppression, and novel brain imaging including delayed myelination, white matter hyperintensity and in one patient at autopsy, putaminal

atrophy. Two further autopsied cases showed hippocampal gliosis and neuronal loss. Two patients had mutations in the KCNT1 gene, while genetic testing for other known early infantile epileptic encephalopathy genes (including PLCB1 and SLC25A22) was negative. (McTague A, Appleton R, Avula S, et al. Migrating partial seizures of infancy: expansion of the electroclinical, radiological and pathological disease spectrum. **Brain** 2013 May;136(Pt 5):1578-91). (Response: Dr R Kneen, University of Liverpool. E-mail: rachel.kneen@liverpool.ac.uk).

COMMENT. Investigators at the Children's Hospital Boston found that loss of PLCB1 function is one cause of malignant migrating partial seizures in infancy (MMPEI), but screening of further cases for PLCB1 deletions or mutations was negative. (Poduri SA, et al. **Epilepsia** 2012 Aug;53(8):e146-50).

Investigators at University of Melbourne, Australia, screened 15 unrelated children with migrating partial seizures of infancy (MPSI) for mutations in several genes associated with infantile epileptic encephalopathies. One patient had a de novo SCN1A missense mutation, and MPSI is the most severe SCN1A phenotype to-date. Epilepsies associated with SCN1A mutations range in severity from febrile seizures to severe epileptic encephalopathies including Dravet syndrome and severe infantile multifocal epilepsy. (Carranza RD, et al. **Neurology** 2011 Jul 26;77(4):380-3).

Nordli DR at Lurie Children's Hospital of Chicago, in discussing epileptic encephalopathies in infants and children, notes that similar gene mutations have been found in several different epilepsy syndromes, and accurate classification of these severe epilepsies is important as the first step toward improved treatment and outcome. (Nordli DR Jr. **J Clin Neurophysiol** 2012 Oct;29(5):420-4).

A complex V *ATP5A1* defect causes fatal neonatal mitochondrial encephalopathy in two siblings reported from Radboud University Medical Centre, Nijmegen Centre for Mitochondrial Disorders, The Netherlands. (Jonckheere AI, Renkema GH, Bras M, et al. **Brain** 2013 May;136(Pt 5):1544-54). Exome sequencing revealed a heterozygous mutation in the *ATP5A1* gene.

***ADORA2A* polymorphism predisposes children to encephalopathy** with febrile status epilepticus in a study of 85 patients with acute encephalopathy. AA diplotype of *ADORA2A* is associated with a higher risk of developing seizures and excitotoxic brain damage. (Shinohara M, Saitoh M, Nishizawa D, et al. **Neurology** 2013 Apr 23;80(17):1571-1576).

INFECTIOUS DISORDERS

ACUTE CEREBELLAR ATAXIA AND LYME DISEASE

Child neurologists at Baskent University Faculty of Medicine, Turkey, report the case of a 5-year-old girl from the Mediterranean region of Anatolia with a 4-day history of progressive ataxia. History of fever, rash or tick bite was absent. Neurologic examination revealed cerebellar signs without signs of meningitis or cranial nerve involvement. CT and MRI were normal and CSF showed a mild pleocytosis and normal protein and glucose. Serological evaluation for Borrelia burgdorferi was positive and IV

cefotaxime was begun. Serum markers for other infectious diseases sometimes complicated by cerebellar ataxia were negative; these included herpes simplex, cytomegalovirus, varicella zoster, mumps, rubella, rubeola, Epstein-Barr virus, and mycoplasma. At discharge on day 28, the neurologic exam was normal, and serum for B burgdorferi IgM and IgG antibodies was positive. (Erol I, Saygi S, Alehan F. Acute cerebellar ataxia in a pediatric case of Lyme disease and a review. **Pediatr Neurol** 2013 May;48(5):407-10). (Resp: Dr Erol, Adana, Turkey. E-mail: ilknur_erol@yahoo.com).

COMMENT. Neuroborreliosis presents with both central and peripheral nervous system manifestations, including aseptic meningitis, meningoencephalitis, Bell's palsy, radiculoneuritis, and myelitis. Four previously published reports of cerebellar ataxia with Lyme disease are reviewed.

MRI AS ADJUNCT IN DIAGNOSIS OF MENINGITIS

Investigators from the Children's Hospital of Pittsburgh, PA, reviewed the literature on the role of MRI as an adjunct for diagnosing meningitis. Of 7 relevant articles, two were reviews and an opinion of usefulness of the MRI was based on 5 articles. Specificity of MRI (i.e. negative imaging findings in those who did not have meningitis) was high and ranged from 93% to 100%. Sensitivity of the MRI was more variable (9%, 85%, 95% and 100%); sensitivity may be higher for bacterial and fungal meningitis than for viral meningitis, but it may depend on the degree of inflammatory response and may vary with etiology. The MRI sequences may vary in yield, the contrast-enhanced FLAIR being most useful in a number of studies. Most of the studies included children, but the majority involved adults.

Based on the studies reviewed, MRI is not recommended to rule out meningitis due to its poor sensitivity; it may be more useful for bacterial compared to viral meningitis, but sensitivity varies depending on MRI technique used and data are limited. MRI is more specific but cannot be recommended to rule in meningitis because data are limited for children and none for infants. (Upadhyayula S. Is there a role for MRI as an adjunct for diagnosing bacterial meningitis? **Arch Dis Child** 2013 May;98(5):388-90). (Response: Dr Shankar Upadhyayula, Infectious Diseases, Children's Hospital of Pittsburgh, PA 15206. E-mail: Shankar.upadhyayula@chp.edu).

COMMENT. If further studies provide a more definitive role, MRI could be of diagnostic value in neonates and small children with traumatic lumbar punctures, to avoid unnecessary long-term antibiotics and extended hospital stay.

NEUROCUTANEOUS DISORDERS

GM1 GANGLIOSIDOSIS TYPE 1 AND MONGOLIAN SPOTS

Investigators in Sao Paulo, Brazil, report a female infant born at term to healthy consanguineous parents who was examined at 9 months for delayed development. She showed hepatosplenomegaly, and widespread Mongolian spots extending over the back

and upper and lower extremities. Funduscopic examination revealed cherry red spot of the retina, consistent with a diagnosis of the lysosomal disease, GM1 gangliosidosis type 1. (Hackbart BA, Arita JH, Pinho RS, Masruha MR, Vilanova LCP. Mongolian spots are not always a benign sign. **J Pediatr** 2013 May;162(5):1070). (Response: Dr Barbara A Hackbart, Division of Child Neurology, Federal University of Sao Paulo, Brazil).

COMMENT. The Mongolian spots result from entrapment of melanocytes in the dermis because of arrested transdermal migration from the neural crest into the epidermis. Hurler syndrome and GM1 gangliosidosis type 1 are diseases associated with generalized Mongolian spots. Infants with GM1 gangliosidosis type 1, also known as Pseudo-Hurler's disease, show facial abnormalities that include frontal bossing, depressed nasal bridge, macroglossia, large low-set ears, and marked hirsutism. About 50% have cherry-red spots. The association of Mongolian spots with the lysosomal disease GM1 gangliosidosis type 1 was not recorded in older neurology textbooks, but a PubMed search found 10 references in the last 30 years (Weissbluth M, et al. **Br J Dermatol** 1981 Feb;104(2):195-200) (Ashrafi MR, et al. **Pediatr Neurol** 2006 Feb;34(2):143-5). Mongolian spots when unusually numerous should prompt an examination for the lysosomal disease, GM1 gangliosidosis type 1.

DEMYELINATING DISEASES

DIAGNOSTIC CRITERIA FOR PEDIATRIC MS

Investigators at Northwestern University Feinberg School of Medicine and Ann & Robert H. Lurie Children's Hospital of Chicago review the diagnostic criteria for pediatric multiple sclerosis, the differential diagnosis, the 2010 McDonald criteria, and Callen criteria. Of all persons with MS, 2% to 5% have onset before 16 years of age. The diagnosis is clinical, requiring recurrent episodes of CNS demyelination, serial changes in MRI lesions, and CSF oligoclonal bands or elevated IgG index. MS must be differentiated from ADEM, neuromyelitis optica and other inflammatory, infectious or metabolic conditions. These include mitochondrial disorders, leukodystrophy, Alexander's disease, MELAS, Kearn-Sayre syndrome, Behcet and Sjogren syndromes, sarcoidosis, Hashimoto's encephalitis, HIV, herpes virus, neuroborreliosis, mycoplasma, the arteriopathy CADASIL, and CNS vasculitis. (Rubin JP, Kuntz NL. Diagnostic criteria for pediatric multiple sclerosis. **Curr Neurol Neurosci Rep** [Section Editor, Nordli DR Jr] 2013 Jun;13(6):354).

COMMENT. In this excellent and comprehensive review, the differentiation of MS from ADEM and other inflammatory or infectious conditions is stressed. Transient demyelinating events must be distinguished from a life-long diagnosis of MS.

Cerebral venous thrombosis (CVT) after LP and steroids in childhood MS. The association between CVT and MS is reported in a 13-year-old girl admitted with left hemiparesis, ataxia, and headache following vaccination against meningococcal group C and hepatitis A. LP and high dose corticosteroids for MS may have contributed to the CVT (Presicci A, et al. **Brain Dev** 2013 Jun;35(6):602-5).