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

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HEADACHE DISORDERS

SLIT VENTRICLE SYNDROME AND HEADACHE

The management of slit ventricle syndrome and shunt-related headache is reviewed by researchers at the Barrow Neurological Institute, St Joseph's Hospital, Phoenix, AZ. Five syndromes of shunt-related headache are described: 1) Intracranial hypotension with headache that develops later in the day and with the erect position and is relieved by lying down. Treatment involves replacement of the valve mechanism and incorporating a device that retards CSF siphoning (DRS), 2) Intermittent proximal obstruction with sudden increase in intracranial pressure (ICP) with activity. As ICP increases, the headache worsens until the ventricular catheter reopens and the pressure is normalized. In chronically shunted patients, proximal shunt failure is most commonly caused by over-drainage of CSF and collapse of the ventricular walls around the catheter. The valve and DRS system are replaced. 3) Normal volume hydrocephalus with symptoms of ICP and headaches developing in the morning and progressing, a common problem with congenital hydrocephalus. All have elevated venous sinus pressure. Older patients have symptoms of pseudotumor cerebri. Treatment involves lumboperitoneal or cisternal shunt. 4) ICP with working shunt associated with Chiari I malformation and hindbrain herniation. Some cases are associated with craniofacial abnormalities and cephalocranial disproportion. 5) Migraine headaches complicating shunted hydrocephalus may require ICP monitoring to exclude slit ventricle syndrome as the cause of headache. The author estimates that one third of his patients with shunted hydrocephalus followed more than 5 years will have chronic headache disorder requiring intervention. In 20% of cases of shunt-related headache the ventricles do not enlarge with shunt failure and the headaches are associated with normal volume hydrocephalus. (Rekate HL. Shunt-related headaches: the slit ventricle syndromes. Childs Nerv Syst April 2008;24:423-430). (Dr HL Rekate, Neuroscience Publications, Barrow Neurological Institute, 350 West Thomas Road,

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Phoenix, AZ 85013. E-mail: harold.rekate@bnaneuro.net).

COMMENT. The cause of headache in shunted hydrocephalus is often not identified with a CT scan. Headache relieved by lying down may point to over-drainage of CSF, intracranial hypotension and slit ventricle syndrome. Headache exacerbated by exercise points to an intermittent obstruction of CSF flow. If the ventricles do not expand with shunt failure, a normal volume hydrocephalus with increased ICP is suspected. All require immediate neurosurgical intervention. Seizures are an additional complication of slit ventricle syndrome. The development of spike and sharp wave EEG abnormality following a shunting operation for hydrocephalus may indicate shunt malfunction and over-drainage of CSF. (Saukkonen A et al. Child's Nerv Syst 1988;4:344-347; Ped Neur Briefs May 1989).

SEIZURE DISORDERS

GENETICS OF FEBRILE SEIZURES AND EPILEPSY (GEFS+)

Mutations in 3 genes SCN1A, SCN1B and GABRG2 have been shown to cause GEFS+ in families of various ethnic origins. The occurrence of mutations in these genes in 19 families of Scandinavian origin with a history of GEFS+ was studied at Ulleval University Hospital, Oslo, Norway, and centers in Denmark. Families were identified from population-based twin registries in Denmark and Norway. One mutation in SCN1A was identified in a Danish family with phenotypes consistent with GEFS+. The mutation was not found in healthy and unrelated controls. No mutations were found in any of the other families. (Selmer KK, Egeland T, Solaas MH et al. Genetic screening of Scandinavian families with febrile seizures and epilepsy or GEFS+. Acta Neurol Scand April 2008;117:289-292). (Respond: Dr Keja K Selmer, Ulleval University Hospital, Kirkeveien 166, 0407 Oslo, Norway).

COMMENT. GEFS+ is an autosomal dominant disorder characterized by multiple febrile seizures persisting beyond age 5 years and complicated by afebrile seizures of absence, myoclonic or atonic types. Seizures cease in mid-childhood. (Scheffer IE et al. **Brain** 1997;120:479-490; Idem. **Epilepsia** 2005;46:41-47). Genes on chromosomes 2q24 and 19q13 encode subunits of the voltage-gated sodium ion channels, while the gene on 5q31 codes for the g-subunit of the g-aminobutyric acid (GABA) receptor. The genes responsible for GEFS+ show considerable heterogeneity and variable expressivity. GEFS+ is an evolving composite of many syndromes, with shared genetic susceptibility. (Nordli DR Jr. **Epilepsia** 2005;46(Suppl 9):48-56). While the definition of GEFS+ is continually changing and probably involves many genes, the common denominator is the association with febrile seizures.

Failure of replication of epilepsy gene associations is discussed by researchers from Columbia University Medical Center, and New York State Psychiatric Institute, New York, NY. (Pal DK, Strug LJ, Greenberg DA. Epilepsia 2008;49:386-392). Over 50 genetic associations with various idiopathic epilepsy syndromes are reported but most have not been replicated. Genetic heterogeneity is a confounder in population-based studies, in both

association and linkage studies. Linkage, association, and mutation analyses are the most common methods of evaluating candidate genes in epilepsy. The authors advocate the integration of results from different experimental methods rather than insisting only on replication.

Discovery of susceptibility genes and their association with drug responsiveness and sideeffects should permit new diagnostic and therapeutic options in the management of the epilepsies. (Helbig I, Scheffer IE, Mulley JC, Berkovic SF. Navigating the channels and beyond: unravelling the genetics of the epilepsies. Lancet Neurol March 2008;7:231-245).

COGNITIVE IMPAIRMENT IN TUBEROUS SCLEROSIS COMPLEX

Seizure histories, EEG recordings and intelligence equivalents and their relation to tuber/brain proportion (TBP) measured by 3 dimensional MRI were evaluated in 61 patients with tuberous sclerosis complex (TSC), in a study at University Medical Center, Utrecht, the Netherlands. Mean age at examination was 17.9 (range 1.6 to 59) years, with 20% of patients age 5 years or less. Diagnosis was confirmed by mutation analysis in 44 (TSC1 mutation in 14 and TSC2 mutation in 30 patients). Seizures occurred in 51 (85%) patients, including infantile spasms in 21 (40%). Age at seizure onset was 1 day to 37 years (mean 2.2 years). EEG epileptiform activity in 46 (79%) patients was unifocal in 16 and multifocal in 30. Tubers detected in all patients numbered from 7 to 58 (mean 28). The mean TBP was 1.3% (range 0.2-5.1%). Intelligence equivalent (IE) ranged from 7-119 (mean 69). IE was below average (<90) in 48 (81%) patients and severely below average in 46 (78%) patients.

Number of tubers was not related to age at seizure onset, infantile spasms, or cognitive function. In contrast, TBP was inversely related to age at seizure onset and cognitive function. Patients with a below average IE had a TBP >1%, and those with above average IE had a TBP <1%. Patients with epilepsy had a lower IE than those without epilepsy. Earlier seizure onset, infantile spasms, and a TSC2 mutation were associated with a lower IE and lower cognition index. (Jansen FE, Vincken KL, Algra A et al. Cognitive impairment in tuberous sclerosis complex is a multifactorial condition. **Neurology** March 2008;70:916-923). (Reprints: Dr FE Jansen, Department of Neurology, C03236, University Medical Centre, PO Box 85500 GA Utrecht, the Netherlands). E-mail: <u>fe_jansen/gumeutrecht.nl</u>

COMMENT. The incidence of seizures and below average intelligence in patients with tuberous sclerosis is 85 and 81%, respectively. Mental retardation (IQ <70) occurs in approximately 50%. Patients with TSC2 mutation are younger at seizure onset, are more cognitively impaired, have more tubers, and have a greater TBP. The proportion of the total brain volume occupied by tubers (TBP) in patients with tuberous sclerosis is a better predictor of cognitive function than tuber number. Age at seizure onset is an independent determinant of cognitive function. The findings point to the importance of aggressive therapy and early seizure control in the management of tuberous sclerosis complex complicated by infantile spasms. Patients with infantile spasms generally have better outlook when treated early. ACTH has a beneficial response in 80% of patients less than one year of age and in 22% when diagnosis and treatment are delayed after one year. (Millichap IG, Bickford RG.

Infantile spasms, hypsarrhythmia, and mental retardation. Response to corticotropin and its relation to age and etiology in 21 patients. **JAMA** 1962;182:523-527).

The phenotypes of tuberous sclerosis patients with TSC1 and TSC2 mutations are compared in an editorial (Nass R, Crino PB. Neurology 2008;70:904-905). Cognitive impairments are more frequent in patients with TSC2 mutation, but are not always more severe than in those with a TSC1 mutation. Only the TSC2 group has a bimodal IQ distribution, with a lower peak around 50 and a higher peak around 80. TSC2 (tuberin) gene mutations generally produce more severe neurologic disease than TSC1 mutations. TBP may prove relevant to the autistic as well as general cognitive phenotype of tuberous sclerosis complex.

BEHAVIOR AND LANGUAGE DISORDERS

AUTISM AND HYDROXYGLUTARIC ACIDURIA

A 3-year-old boy with L-2-hydroxyglutaric aciduria (HGA) who demonstrated severe autistic symptoms is reported from Aristotle University of Thessaloniki, Greece; VU University, Amsterdam, the Netherlands; and University Hospital, Heidelberg, Germany, The child was seen at age 4 months because of macrocephaly, noted on in utero ultrasound. He was born with esophageal atresia. Neurologic examination revealed hypotonia, hyperreflexia, and psychomotor retardation. EEG and BAEPs were normal, whereas visual evoked potentials showed prolonged latencies. Brain MRI showed diffuse subcortical encephalopathy with increased signal of subcortical white matter. Metabolic leukodystrophy was suspected. Urinary organic acid analysis showed increased levels of L-2-HGA, and DNA analysis demonstrated 2 missense mutations in the gene L-2-HGDH encoding L-2-HG dehydrogenase. Motor development was moderately impaired, walking at age 19 months, whereas speech development was severely impaired, saving only single words at age 2 years and no phrases at 3 years. Stereotypies including arm flapping and finger wiggling began at age 12 months, repetitive behaviors and movements at age 2, and poor eye contact, aloofness, and absent communication by age 3 years. He reacted with tantrums to any change in his routine. The CARS score was 44/60, indicative of severe autism, Repeat MRI shows progression of white matter changes, and head circumference remains above the 97th percentile (54 cm). (Zafeiriou DI, Ververi A, Salomons GS et al. L-2-hydroxyglutaric aciduria presenting with severe autistic features. Brain Dev April 2008;30:305-307). (Respond: DI Zafeiriou. E-mail: jeff@med.auth.gr).

COMMENT. L-2-hydroxyglutaric aciduria is an autosomal recessive neurometabolic disorder characterized by psychomotor delay, ataxia, macrocephaly, and MRI changes of leukoencephalopathy. L2HGDH is the disease-causing gene that encodes L-2-HG dehydrogenase. The authors found no previous reference to autism as a feature of the L-2-HGA phenotype. Nonspecific MRI changes reported in autism include cerebellar vermal hypoplasia. (Courchesne E et al. Neurology 1994;44:214-223).

LANGUAGE DISORDER AND POLYMICROGYRIA

The co-occurrence of developmental language disorder and reading impairment in members of three families with perisylvian polymicrogyria is reported from the State University of Campinas, and University of Sao Paulo, Brazil. The severity of language impairment correlated with the extent of the polymicrogyria, patients with the worst language deficit having diffuse bilateral perisylvian polymicrogyria while patients with mild impairment showing subtle MRI anomalies. (Oliveira EPM, Hage SRV, Guimares CA et al. Characterization of language and reading skills in familial polymicrogyria. **Brain Dev** April 2008;30:254-260). (Respond: Dr MM Guerreiro: E-mail: <u>mmg@fcm.unicamp.br</u>).

COMMENT. Polymicrogyria is a cerebral developmental anomaly, characteristically perisylvian in location, giving the cortical surface a pebbled, 'chestnut kernel,' or 'Moroccan leather' appearance. Genetic or acquired causes are described. A causative diagnosis was established in 20 of 48 cases recently reported (de Wit MCY et al. Arch Neurol March 2008;65:358-366; Ped Neur Briefs March 2008;22:24). A genetic cause was suspected in 6 patients with multiple congenital abnormalities and in 4 with consanguineous parents or multiple affected family members. A gestational insult was the probable cause in 7 patients. Polymicrogyria can be localized or diffuse, unilateral or bilateral. The cortex is thickened, without recognizable layers or with 4 layers in place of the usual 6. The brain stem may be hypoplastic, especially involving the pyramidal tracts. In severe cases, the child has spastic diglegia or hemiplegia, mental retardation, and seizures. The MRI has permitted the diagnosis and recognition of milder forms of polymicrogyria, some associated with language and reading disorders, as described in the above study.

NONAUTISTIC MOTOR STEREOTYPIES

Clinical features and long-term outcomes of 100 children (62 boys and 35 girls) with motor stereotypies were evaluated by review of records and telephone interviews at Johns Hopkins Hospital, Baltimore, MD. Mean age was 8.3 +/- 4.5 years. Age at onset was < 24 months in 81%. All children were in a regular classroom and were at least grade C in achievement. Six had a history of early language delay. Repetitive, rhythmic, involuntary movements consisted of finger wiggling and/or flapping of hands or arms; 20% also exhibited facial grimacing, and 8% had head nodding movements. Movements occurred once a day or more in 90% and lasted less than a minute in 62%. Triggers included excitement/happiness in 80%, anxiety and stress in 26%, and fatigue in 21%. Stereotypies ceased during sleep and when cued by calling his or her name. Family history was positive for most motor stereotypies in 17% first-degree relatives, but negative in patients with head nodding. Associated conditions included ADHD in 30%, tics in 18%, and OCD in 10%. Various medications prescribed in 20 patients, including clonidine, risperidone, and oxcarbazepine, were ineffective, and behavior modification in 14 resulted in modest improvements in 5 patients. Follow-up ranged from 2 months to 26 years, with a median of 6 years. Movements were persistent in 94 children, continuing for >10 years in 22%, and 6-10 vears in 44%. Prognosis was better in children with head nodding than in those with hand/arm movements; head nodding resolved in one third, compared to only 3% with hand movements (P=0.001). (Harris KM, Mahone EM, Singer HS. Nonautistic motor stereotypies: clinical features and longitudinal follow-up. **Pediatr Neurol** April 2008;38:267-272). (Dr Singer, Division of Pediatric Neurology, Department of Pediatrics, Johns Hopkins School of Medicine, Child Health Building, 200 N Wolfe St, Suite 2158, Baltimore, MD 21287).

COMMENT. The present findings in 100 patients are similar to those reported in a previous study of 40 patients from the same institution (Mahone EM et al. J Pediatr 2004;145:391-395; Ped Neur Briefs Sept 2004;18:72). Most motor stereotypies are chronic and persistent and of greater concern to parents and physicians than to the child. Approximately 50% of patients with motor stereotypies >7 years of age have a comorbid disorder such as ADHD, tics or OCD.

Motor stereotypies are defined as involuntary, bilateral, repetitive, rhythmic movements associated with periods of excitement, stress, and fatigue. (Castellanos FX et al. J Clin Psychiatry 1996;57:116-122). They are common in mentally retarded and autistic children, and less prevalent in otherwise normal, healthy children. Associated disorders such as tics are distinguished by a later age of onset, 5-10 years, their asymmetry, vocal as well as motor, and response to medication.

NEUROMUSCULAR DISORDERS

CONGENITAL FIBER TYPE DISPROPORTION GENETICS

Novel heterogeneous missense mutations in five families with congenital fiber type disproportion (CFTD) were identified in a study at Children's Hospital at Westmead, University of Sydney, and other centers in Australia, Canada, and France. In 11 affected patients with TPM3 gene mutations and CFTD, symptoms of hypotonia presented in the first year. Some had a "dropped head" posture while crawling. Five walked late at 18 - 60 months, while 6 walked at a normal age. Most improved functionally until adolescence, when motor ability stabilized or slowly declined. Four patients older than 30 years were still ambulant. Respiratory insufficiency occurred during sleep, despite good limb strength, and ventilatory support was required as early as 3.5 years in one patient and as late as 55 years in one. One died unexpectedly at 45 years old. Spinal changes were invariable, with lumbar lordosis and thoracic kyphosis in early childhood, becoming more severe in late childhood or adulthood. Neck muscle weakness and extensor contractures were common. Most had generalized amyotrophy, proximal limb weakness, and a waddling gait. Mild facial weakness and ptosis, and winged scapula were common. Intellectual function was normal. Cardiac function was normal, except for 1 patient with left ventricular hypertrophy. CK level was low normal and rarely, mildly increased. Nerve conduction studies were normal, and EMG normal or myopathic. In muscle biopsies, type 1 fibers were atrophied and 50% smaller than type 2 fibers. Type 2 fibers were hypertrophied, 1.6 times normal diameter, and 25% had internal nuclei. In a sixth family with TPM3 mutation, some patients had features of CFTD and others had nemaline myopathy. TPM3 mutation is the most common cause of CFTD in reported cases. (Clarke NF, Kolski H, Dye DE et al. Mutations in TPM3 are common causes of congenital fiber type disproportion. Ann Neurol March 2008;63:329-337). (Respond: Prof Kathryn N North, Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW 2145, Australia, E-mail: kathryn(a chw.edu.au).

COMMENT. Congenital fiber type disproportion (CFTD) is a rare cause of congenital myopathy and hypotonia. Clinical features are heterogeneous, and mutations in several genes have been identified. Diagnosis should exclude other causes for myopathy, since type 1 fiber hypotrophy is a common secondary feature in many neuromuscular disorders. The above authors have previously found mutations in ACTA1 and SEPN1 genes in a few patients with CFTD. The present report of TPM3 mutations involving 11 cases in 5 families is the largest series to date. Affected patients present with hypotonia before the first birthdate and show a slow progression of proximal muscle weakness, kyphoscoliosis, and respiratory insufficiency, but most remain ambulant and survive to adulthood.

DIAGNOSTIC APPROACH TO NEONATAL HYPOTONIA

The frequency of various disorders causing neonatal hypotonia and the reliability of the first physical examination and standard diagnostic tests were evaluated by a retrospective review of records of 144 patients diagnosed between 1999 and 2005 at Strasbourg University Hospital, France. Of 120 cases with a final diagnosis of neonatal hypotonia, 82% had central (cerebral) causes, including hypoxic and hemorrhagic brain lesions in 34%, chromosomal abnormalities (eg Prader-Willi syndrome) in 26%, brain malformations in 12%, and metabolic or endocrine diseases in 9%. Peripheral (neuromuscular) causes confirmed in 22 (18%) cases included spinal muscular atrophy in 6% and myotonic dystrophy in 4%. Hypotonia first noticed before the 28th day of life and lasting for at least two weeks was an inclusion criterion. Exclusion criteria were gestational age less than 35 weeks, neonatal infection and congenital heart disease. Initial presentation of hypotonia was classified as central, peripheral or undetermined, according to Dubowitz criteria. Central hypotonic cases had preserved antigravity limb movements, normal or increased peripheral tone, poor visual contact, seizures, and brisk tendon reflexes. Peripheral hypotonia was characterized by muscular weakness, absent antigravity movements, decreased reflexes, global hypotonia, and preserved social interaction. Hypotonia was diagnosed in 4.2% of neonates admitted. Mean age of referral was 11.8 days. Swallowing difficulties affected 101 (70%), and respiratory distress occurred in 79 (55%).

The initial neurologic examination classified hypotonia as central in 87 (60%). peripheral in 40 (28%), and undetermined in 17 cases. The positive predictive value of the first clinical examination was 86% for central hypotonia and 52% for peripheral cases. Among 17 with undetermined initial diagnosis, 14 cases proved to be of central origin. Decreased fetal movements and/or polyhydramnios were reported in 19 pregnancies (13%), and were predictive of a prenatal cause in 15 (p<0.05). Perinatal asphyxia in 77 cases was the cause in 39 cases. At time of follow-up (1 year or longer) 40 (29%) infants had died (22 in the first two months), and 8 (6%) were completely recovered. Risk factors for a higher mortality rate were initial respiratory distress, prolonged feeding difficulties, and neuromuscular causes for hypotonia (p<0.05). Neuroimaging contributed to the final diagnosis in 50 cases, especially for brain malformation (MRI), intracranial hemorrhage (CT), and hypoxic-ischemic encephalopathy. EEG contributed to diagnosis in 35/92 (38%) cases, especially with hypoxic and/or hemorrhagic brain lesions and cortical gyration abnormalities. DNA-based diagnostic tests performed in 43 cases were confirmatory in 18 (42%). Molecular tests in 34 cases confirmed a diagnosis of spinal muscular atrophy in 5, mvotonic dystrophy in 5, and Prader-Willi syndrome in 3 cases. Karyotype analyses in 59 neonates were contributory in 24 (41%). Metabolic tests in 45 cases contributed to the final diagnosis in 9 (20%). EMG and NCS in 23 neonates were contributory in 10, but misleading and incorrect in 3 (spinal muscular atrophy mistaken for demyelinating neuropathy, and negative reports in a case of myotonic dystrophy and one of congenital muscular dystrophy). Muscle biopsy in 14 cases was helpful in 6, and tests for congenital mysthenia in 10 were negative. (Laugel V, Cossee M, Matis J et al. Diagnostic approach to neonatal hypotonia: retrospective study on 144 neonates. **Eur J Pediatr** May 2008;167:517-523). (Respond: Dr Vincent Laugel, Sevice de Pediatrie 1, CHU Strasbourg-Hautepierre, Avenue Moliere, F-67098 Strasbourg Cedex, France. E-mail: <u>wincent.laugel(Art-strasbourg.fr)</u>.

COMMENT. The hypotonic infant is a fairly common pediatric problem, accounting for 1 in 25 admissions to a tertiary medical center and neonatal unit. The authors provide a diagnostic algorithm based on the yield of the initial neurological examination and various tests. Central (cerebral) causes are most frequent, and the initial physical examination has a higher positive predictive value for this type of hypotonia than for peripheral (neuromuscular) types. First line tests to confirm a central cause are neuroimaging and EEG. For peripheral type hypotonia, examination of the mother (in suspected myotonic dystrophy or neonatal transient myasthenia) and DNA-based tests are most reliable. In some cases a longer follow-up may be necessary to determine the course of the disease and the correct diagnosis.

The hypotonic or limp infant syndrome has been reviewed in the literature over many years. (Walton JN. The limp child. J Neurol Neurosurg & Psychiat 1957;20:144-154) (Millichap JG. The hypotonic child. In Practice of Pediatrics. Vol IV, ed. Brennemann-Kelley, Chap 16, Hagerstown, MD; WF Prior Co. 1966). Infants with so-called benign congenital hypotonia, a term coined by Walton, are limp at birth, sitting and walking are delayed, but muscle wasting is not profound. The muscle fibers are generally small for the age. Muscle strength and motor development gradually improve, but mental retardation and other congenital abnormalities are not uncommon. In recent years, molecular genetic diagnosis of myopathies has uncovered several inherited diseases characterized by neonatal hypotonia, including nemaline myopathy and congenital fiber type disproportion (Clarke NF et al. Ann Neurol March 2008;63:320-337) (Rifai Z et al. Neurology 1993;43:2372-2377). Defining the genetic basis of these diseases will explain their heterogeneous clinical manifestations and lead to improvements in family counseling.

MOVEMENT DISORDERS

DOPA-RESPONSIVE DYSTONIA WITH DELAY IN WALKING

A 2-year, 8-month old boy with a previous diagnosis of cerebral palsy was referred to UCSF because of "awkward" gait and "walking on the toes." His gait abnormality progressed, worsening in the evening, and he was found to have a dopa-responsive dystonia caused by an autosomal-dominant GCH1 mutation. He was treated successfully with oral carbadopa-levodopa (Sinemet). Three other family members were affected, presenting with stiffness in the thighs, motor impairment, speech and swallowing difficulties, postural tremor and depressive anxiety, also responsive to carbadopa-levodopa. (Cheyette BNR et al. **Pediatr Neurol** April 2008;38:273-275).