

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@chw.edu.au](mailto:kathryn@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 28<sup>th</sup> 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, myotonic dystrophy in 5, and Prader-Willi syndrome in 3 cases. Karyotype analyses in 59