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NEUROMUSCULAR DISORDERS

NEMALINE MYOPATHY: CLINICAL STUDY

Clinical and genetic characteristics, prognostic risk factors, and classification of nemaline myopathy (NM) are examined in a study of 143 cases identified at two centers in Australia and North America and reported from the Neurogenetics Research Unit, University of Sydney, Australia; Children's Hospital, Boston; and other centers. Of the 143 cases, 23(16%) were typed as *severe congenital NM,* 29(20%) were *intermediate congenital,* 66(46%) *typical congenital,* 19(13%) of *childhood onset,* and 6(4%) of *adult onset.* Severe congenital cases had absence of spontaneous movements and respiration, and contractures (arthrogryposis multiplex congenita (AMC) in 8 cases) and fractures at birth, and 74% died of respiratory insufficiency (1d-1.3y). Intermediate congenital cases presented neonatally (<28 days) with hypotonia, their motor milestones were delayed, they developed contractures (only 1 AMC) in early childhood, they had respiratory symptoms, and were confined to a wheelchair by 11 years, and 28% died (2w-2.9y). Typical congenital cases presented in infancy (usually after 28 days) or early childhood, 1/3 had neonatal hypotonia, weakness was initially proximal and later distal, most were ambulant before 18 months of age, the course was slowly progressive in 23%, and 6% died (6-19y). Childhood onset cases presented with delayed motor milestones and facial diplegia, but diagnosis was delayed for years after onset, and only 5% died (46y). Adult onset cases presented at 41 to 59 years of age, 4(66%) were symptomatic for up to 20 years before diagnosis, all had mild facial and proximal weakness, 4 had myalgia, and none died. Additional symptoms in some congenital cases included food intolerance with gavage feeding and gastrostomy, bulbar dysfunction with dysarthria, drooling and aspiration, cardiac dysfunction, and seizures. Electromyography was abnormal in 42 of 64 patients tested. *Inheritance* was autosomal recessive in 29 cases (20%), autosomal dominant in 41(29%), and sporadic in 72(50%). Risk factors for early mortality, mainly in severe congenital cases, were arthrogryposis, neonatal respiratory failure, and delayed motor milestones. Motor outcome was correlated with respiratory involvement; patients requiring ventilatory support in the first year never walked, In children

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surviving the neonatal period, muscle weakness and respiratory function improved with increasing age. (Ryan MM, Schnell C, Strickland CD et al. Nemaline myopathy: a clinical study of 143 cases. Ann Neurol September 2001;50:312-320). (Respond: Dr Kathryn N North, Neurogenetics Research Unit, Children's Hospital at Westmead (Royal Alexandra Hospital for Children), Department of Paediatrics and Child Health, University of Sydney, Sydney, Australia).

COMMENT. Nemaline myopathy, first described by Shy and coworkers in 1963, is characterized by a slowly progressive, or static weakness and hypotonia of pelvic and other muscles, and threadlike, intracellular rods, staining red with modified trichrome stain, in muscle fibers. The term nemaline is derived from the Greek word *nema* or thread. Inheritance is autosomal dominant, recessive, or sporadic. Clinical classification of nemaline myopathy (NM) is determined by three factors: 1) respiratory function, 2) severity and distribution of weakness, and 3) motor milestones. *Severe congenital* subtype has clearly defined symptoms with a poor outcome. *Intermediate and typical congenital* subtypes are difficult to distinguish in infancy but can be separated in later childhood; patients with *typical congenital* NM crawl before 12 months and walk before 18 months, whereas *intermediate cases* are more delayed, the course is more progressive, and mortality is significantly higher. *Childhood- and adult-onset* cases have overlapping characteristics and a good prognosis. Prenatal expression of NM has been associated with fetal akinesia sequence (Lammens et al, 1997, cited by above authors), and frequent obstetric complications. Mortality, especially in severe and intermediate congenital subtypes, is almost invariably caused by respiratory insufficiency, and motor outcome is correlated with respiratory involvement. After the neonatal period, treatment of pulmonary infection and feeding problems can lower mortality. For earlier references to congenital nemaline myopathy, see Progress in Pediatric Neurology III, PNB Publ, 1997;pp349-351).

METABOLIC DISORDERS

GLUT-1 DEFICIENCY SYNDROME AND FAMILIAL EPILEPSY

A family with autosomal dominant Glut-1 deficiency syndrome (DS) affecting 5 members over 3 generations is reported from the University of Goettingen, Germany; and Columbia University, New York. Clinical and laboratory features of 2 brothers and a mother showed severe to mild seizures (nodding, eye rolling, jerking, and atonia, with loss of consciousness), delayed motor and mental development, severe to mild ataxia-dystonia or clumsiness, hypoglycorrhachia (<40 mg/dl; reduced CSF/blood glucose ratio (0.33, normal, 0.65)), and decreased erythrocyte 3-O-methyl-D- glucose uptake. Deceleration in head growth in early childhood was associated with greater neurological impairment in one brother. Fasting accelerated, whereas feeding carbohydrate delayed, neurological deterioration. Antiepileptic drugs were ineffective, and phenobarbital worsened infantile seizures (phenobarbital inhibits Glut-1 facilitated transport of glucose and dehydroascorbic acid). The ketogenic diet controlled seizures. A heterozygous R126H missense mutation was identified in the 3 patients tested. (Brockmann K, Wang D, Korenke CG et al. Autosomal dominant Glut-1 deficiency syndrome and familial epilepsy. Ann Neurol October 2001;50:476-485). (Respond: Dr Darryl C De Vivo, Department of Neurology, Laboratory for Pediatric Research, Columbia University, New York, NY 10032).