

PEDIATRIC NEUROLOGY BRIEFS

A MONTHLY JOURNAL REVIEW

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

Vol. 18, No. 2

February 2004

NEUROMUSCULAR DISORDERS

DIAGNOSIS OF CONGENITAL MYASTHENIC SYNDROMES

Clinical and neurophysiological data of 11 patients (4 males, 7 females) with congenital myasthenic syndromes (CMS) diagnosed between 1994 and 2000 are reported from Great Ormond Street Hospital, London, UK. Eight presented immediately after birth and 3 by 10 months of age. Common characteristics included profound hypotonia (9/11 patients), arthrogryposis (8), absent tendon reflexes (5), ptosis (7), bulbar signs (8), recurrent apnea or asthma attacks (8), ventilator at birth (7), seizures (3), and poor response to treatment with death at 1–17 months of age (5) or ventilator dependency (2). Four patients survive with motor delay at 8–38 month follow-up. An edrophonium test was positive in 3 of 6 tested, and 8 of 11 responded partially to pyridostigmine. Diagnosis was confirmed by a decrement response after repetitive nerve stimulation or by increased instability and jitter after single fiber EMG stimulation. A positive family history with an undiagnosed neuromuscular disorder and death of at least one previous sibling was obtained in 5 patients. None of the clinical and neurophysiological characteristics was correlated with outcome. Except for one patient with a fast channel CMS, none was classified on a molecular basis as a previously recognized subtype of CMS. (Zafeiriou DI, Pitt M, de Sousa C. Clinical and neurophysiological characteristics of congenital myasthenic syndromes presenting in early infancy. *Brain Dev* Jan 2004;26:47-52). (Repond: Dr Dimitrios I Zafeiriou, Egnatia St 106 54622, Thessaloniki, Greece).

COMMENT. In a series of 51 childhood-onset patients with myasthenia gravis (MG), reported from the Massachusetts General Hospital (Millichap JG, Dodge PR. *Neurology* 1960;10:1007-1014), 35 had juvenile MG with symptoms beginning after the first year of life, 10 born to mothers with MG had neonatal transient myasthenic syndrome, and 6 whose mothers were unaffected had neonatal persistent (congenital) myasthenia. In this earlier

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series of cases, congenital myasthenic syndrome (CMS) was distinguished from the neonatal transient form by absence of MG in the mother, less severe generalized muscle weakness, and a poor response to anticholinesterase treatment. Ptosis, ophthalmoplegia and weakness of facial and masticatory muscles persist through childhood in to adult life. The family history may be positive for MG in siblings and cousins.

Since this clinical description of the congenital myasthenic syndrome in 1960, and the subsequent discovery of an autoimmune mechanism for MG, the absence of antibodies against the acetylcholine receptor further delineate the congenital syndrome. Engel and his colleagues have identified several CMS subtypes, including Lambert-Eaton CMS, end-plate AchE deficiency, slow and fast channel syndromes, and AchR deficiency. (Engel AG, Ohno K. *Adv Neurol* 2002;88:203-215; *Muscle & Nerve* 1993;16:1284-1292). See **Progress in Pediatric Neurology III**, PNB Publishers, 1997;346-349, for further case reports and commentaries on CMS. The identification of subtypes of the CMS is complex and requires studies of the kinetics of acetylcholine receptors (AchR), and ultrastructure of the endplate. Nevertheless, with an increased awareness of the syndrome, a diagnosis can be determined on clinical and neurophysiological grounds, leading to earlier treatment intervention and better genetic counseling.

TREATMENT OF AUTOIMMUNE MYASTHENIA GRAVIS

A treatment protocol for autoimmune myasthenia gravis (MG), patients sero-positive for AChR antibodies, is proposed from the University of California, Davis, CA. The greatest advances in outcome have resulted from therapies that reduce the autoimmune attack or modify its effect on the nicotinic acetylcholine receptor (AChR) and prevent damage to the structure of the endplate. More effective symptomatic treatment, including critical care and the use of cholinesterase inhibitors, has contributed to an improved prognosis. The initial therapy is determined on an individual cost/benefit ratio. Cholinesterase inhibitor drugs, first introduced in 1934 (Walker MB. *Lancet* 1934;1:1200-1201), and especially pyridostigmine, are usually effective early in the disease course or in mild cases. Tolerance develops and eventually the effect lessens even at maximal, frequently toxic, doses. The more effective treatments directly target the autoimmune response, reducing the likelihood of endplate damage. Immuno-directed treatment should begin when an early spontaneous remission is not obtained with pyridostigmine. High-dose daily prednisone is started, and short-term IV Ig or plasmapheresis is added if symptoms worsen in the first 2 weeks, or given concomitantly. Tapering of the prednisone is begun slowly when remission is established. Later, a steroid-sparing agent (eg azathioprine) and a bisphosphonate to prevent osteoporosis are added to the low-dose prednisone. The minimum amount of prednisone to maintain a remission is the goal in management. Thymectomy also acts as a steroid-sparing treatment and facilitates remission. Uncontrolled studies show that the earlier the operation, the better the result, and newer surgical techniques may carry less risk. The goal for optimal therapy is an increased specificity of immune-directed agents that reduce the antibodies or T-cell responses to the AChR, leaving other immune responses intact. (Rishman DP, Agius MA. Treatment of autoimmune myasthenia gravis. *Neurology* December (2 of 2) 2003;61:1652-1661). (Reprints: Dr David P Richman or Mark A Agius, University of California, One Shields Avenue, Davis, CA 95616).