Light on limb-girdle myasthenia

In the current issue of *Brain*, Slater *et al.* (2006) describe their findings in eight patients in seven kindreds suffering from limb-girdle myasthenia (LGM). All eight had progressive weakness in a proximal limb-girdle distribution that began in the first or second decade of life, a decremental EMG response on 3 Hz stimulation and a favourable response to anticholinesterase medications. The ocular muscles were spared except for slight facial weakness and ptosis in some patients. None had short-term fatigability induced by exercise, and none had detectable anti-AChR antibodies. Thus, they differed from most myasthenic patients in whom ocular involvement heralds the onset of the disease and who typically experience increased weakness after exercise. In addition to thoroughly describing the clinical features of their patients, Slater *et al.* also investigated each patient by intracellular microelectrode studies of neuromuscular transmission and by quantitative light and electron microscopy analysis of the structure of the neuromuscular junction (NMJ).

Although the clinical, electrophysiological and morphological findings in the LGM patients observed by Slater *et al.* were similar, the authors indicate that LGM may encompass a heterogeneous group of conditions. To date, no fewer than 61 patients in 36 kindreds have been reported under the rubric of LGM (McQuillen, 1966; Johns *et al.*, 1971, 1973; Wolters and Leeuwin, 1976; Dobkin and Verity, 1978; Oh and Kuruoglu, 1992; Azulay *et al.*, 1994; Vasant *et al.*, 1994; Furui *et al.*, 1997; Zephir *et al.*, 2001; Rodolico *et al.*, 2002; Shankar *et al.*, 2002; Slater *et al.*, 2006). Sparing of the ocular muscles, proximal limb-girdle distribution of the weakness, a decremental EMG response and responsiveness to anticholinesterase medications appear to be common features of LGM. Consistent with recessive inheritance in some patients, more than one offspring was affected in 27 kindships, and in seven families the parents were consanguineous. Despite these clinical similarities, divergent phenotypic features were also present. Short-term fatigability on exertion was not a feature of Slater’s patients but was observed in other patients (McQuillen, 1966; Johns *et al.*, 1971; Dobkin and Verity, 1978; Colomer *et al.*, 2006). Tubular aggregates arising from the sarcoplasmic reticulum were detected in most patients who had muscle biopsies (Johns *et al.*, 1973; Dobkin and Verity, 1978; Azulay *et al.*, 1994; Furui *et al.*, 1997; Zephir *et al.*, 2001; Rodolico *et al.*, 2002; Colomer *et al.*, 2006) but were conspicuous in only one of Slater’s patients. Mild elevations of the serum creatine kinase level (Furui *et al.*, 1997; Zephir *et al.*, 2001; Rodolico *et al.*, 2002) and EMG findings suggesting a myopathy (Oh and Kuruoglu, 1992; Azulay *et al.*, 1994; Zephir *et al.*, 2001; Rodolico *et al.*, 2002) were described in some but not all patients. Abnormal electrical irritability of the muscle fibres and features of an arrhythmogenic cardiomyopathy were found in three sisters (Dobkin and Verity, 1978) but not in others. These divergent phenotypic features imply phenotypic as well as genetic heterogeneity of LGM.

Two publications before 1976 described LGM in a familial setting (McQuillen, 1966; Johns *et al.*, 1973). All LGM patients reported after 1976 had been tested for anti-AChR antibodies. Among these, 5 of the 12 patients investigated by Oh and Kuruoglu (1992), 4 of the 9 observed by Rodolico *et al.* (2002) and 1 of 3 described by Azulay *et al.* (1994) had a low titre of anti-AChR antibodies. Moreover, another of Azulay’s patients with an insignificant titre of anti-AChR antibodies improved when treated with high doses of intravenous immunoglobulins. Most autoimmune LGM patients presented after the third decade of life, and three of Rodolico’s patients also had thymoma. These findings mandate that all sporadic LGM patients should be tested for anti-AChR antibodies and have high-resolution imaging of the mediastinum to exclude thymic enlargement or thymoma. However, even negative tests for anti-AChR antibodies do not fully exclude autoimmune LGM because of the low titre of anti-AChR antibodies in this disorder, and because anti-AChR antibodies can be absent in some patients with autoimmune myasthenia gravis. This implies that a trial with immunosuppressive medications should be considered in sporadic seronegative LGM, and especially in patients presenting after the second decade of life.

A remarkable aspect of the article by Slater *et al.* is the skill with which they dissected the pathogenesis of LGM in their patients. Myasthenic disorders arise when the safety margin of neuromuscular transmission is compromised by one or more specific mechanisms. The safety margin is determined by the difference in post-synaptic depolarization caused by the end-plate potential (EPP) and the depolarization required to activate the voltage-sensitive sodium channels deployed in segments of the post-synaptic membrane that line the depths of the secondary synaptic clefts. The amplitude of the EPP is determined by the amplitude of the miniature EPP (MEPP) and the number of quanta released by nerve impulse (m). In the LGM patients investigated by Slater, the mean amplitude of the EPP was reduced to 47% of normal, which would impair the safety margin of neuromuscular transmission. The mean amplitude of the MEPP was 69% of normal and that of m was decreased to 59% of normal. The combined decrease of these two values...
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et al.
known. Slater

could be identified by haplotype analysis.

LGM. A possible reason for the higher prevalence of LGM
among myasthenic patients observed by Oh in
the Newcastle area of England, it was
Although LGM accounted for a high proportion of children
of the category of congenital myasthenic syndromes (CMS).

The nerve–muscle contact area at the LGM junction was
only half of that found in the controls, but the mean diameter
of the LGM muscle fibres was ~12% larger than that in
the controls; thus the LGM junctions were inappropriately small
for the size of the muscle fibres. The total number of AChRs
per junction was reduced in proportion to the size of the
junction. Therefore, the density of receptors as well as quantal
release per unit area of synaptic contact could be assumed
to be normal. Finally, ultrastructural analysis of the post-
synaptic region showed that the junctional folds were shorter
and simpler than normal or even absent at some junctions.
On the basis of these observations, the decreased amplitude of
the MEPP is readily explained by the increased muscle fibre
size and simplification of the junctional folds, both of which
will reduce the input resistance at the NMJ. The reduced size
of the junction, and presumably of the total number of
synaptic vesicles available for release, probably contributes
to the decreased quantal release by nerve impulse.

It is now clear that the non-immune forms of LGM fall in
the category of congenital myasthenic syndromes (CMS).
Although LGM accounted for a high proportion of children
with myasthenia in the Newcastle area of England, it was
uncommon among myasthenic patients observed by Oh in
the United States and by Rodolico in Sicily. Among the
248 CMS patients investigated at the Mayo Clinic, only
7 (2.8%) were ultimately diagnosed as suffering from
LGM. A possible reason for the higher prevalence of LGM
in the Newcastle area would be a common founder that
could be identified by haplotype analysis.

The molecular cause of LGM in Slater’s patients is not yet
known. Slater et al. have excluded currently recognized
molecular causes of the CMS. That the LGM NMJ is under-
developed points to a factor that selectively regulates the
development or maintenance of the NMJ in the limb-
girdle but not in the oculobulbar muscles. Targeted gene
analysis or linkage analysis of a sufficient number of informative Newcastle kinships with a clinically similar
form of LGM would be a logical next step in defining the
aetiology of this interesting syndrome.

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