SCIENTIFIC COMMENTARY

Light on limb-girdle myasthenia

In the current issue of *Brain*, Slater *et al.* (2006) describe their findings in eight patients in seven kinships 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 muscle 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 kinships 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, their patients presented after the second 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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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 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 postsynaptic 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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References


