Advances in Myasthenia Gravis

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Introduction
Autoimmune myasthenia gravis (MG) is probably the best understood of the human autoimmune diseases [1], and our knowledge of its pathogenesis and treatment has increased dramatically in the past 20 years. In this article, we review recent advances in the epidemiology, evaluation, diagnosis, and treatment of this fascinating disease.

Current Trends in the Epidemiology of Myasthenia Gravis
Worldwide population-based studies of the epidemiology of MG show that the prevalence of MG has increased from 1950 to the 1990s, and the slope for prevalence is significantly steeper than that for incidence. The smaller number of available mortality rates in the literature makes the analysis less powerful, but there was a trend toward a lower death rate for MG during this period [2]. Improved diagnostic techniques and epidemiologic methodology certainly play a role, but the primary factor appears to be an increased life span after diagnosis. The number of MG patients worldwide is increasing steadily compared with rheumatoid arthritis and systemic lupus erythematosus, for which incidence rates are stable. A significant increased incidence of MG in the elderly population has been demonstrated, and over 60% of all patients with MG in the United States are now over 50 years of age. Several observations support the hypothesis that late-onset MG is different from early-onset MG. Thymomas are much more common in older patients. The more severe prognosis of late-onset MG is thought to be related to immunologic factors because the patients with or without thymoma are rarely DR3 positive and frequently have anti-titin antibodies [3]. A hypothetical immune-mediated myopathy associated with antistriated antibodies in late-onset MG may contribute to the increased weakness and poorer prognosis in these patients [4]. Treatment of late-onset MG can be challenging, as there are more complications from plasmapheresis in the elderly, side effects of immunosuppressive medication are frequently more serious in this age group, and the response to thymectomy may be poorer than in younger patients.

To clarify whether the generally accepted 2:1 female-to-male ratio in MG prevalence is also valid for disease incidence, Poulas et al. [5] analyzed 601 seropositive patients with disease onset between 1983 and 1998 in Greece. The incidence ratio was 1:1, and it was concluded that MG affects men and women equally, despite the unequal prevalence [5].

What's New for the Diagnosis of Myasthenia Gravis?
The diagnosis of MG is largely based on the typical history of fluctuating diplopia, ptosis, dysarthria, and limb weakness, and on the objective fatigable weakness found on manual muscle testing. Repetitive nerve stimulation (RNS) is the most commonly used and available confirmatory physiologic test, and is reported to have a sensitivity of 89% in generalized MG and 68% in ocular myasthenia when performed in multiple muscles. The facial and spinal accessory nerves are the most commonly tested cranial nerves, but they are not ideal in evaluating patients with predominant dysphagia. Pavesi et al. [6] reported a simple method for RNS in the masseter muscle and obtained normative data. The test is easy to perform, reproducible, and well tolerated. Masseteric RNS showed a greater decrement than RNS in the ulnar or accessory nerve and should be considered in the electrophysiologic evaluation of MG patients, especially when bulbar symptoms are prominent.

There is currently no method to predict which ocular MG (OMG) patients will progress to generalized MG (GMG). Two recent studies addressed the hypothesis that
single-fiber electromyogram (SFEMG) measurement of jitter in a forearm muscle, the extensor digitorum communis (EDC), performed at the time of presentation can predict the progression from OMG to GMG. Weinberg et al. [7•] studied 39 patients prospectively and showed that 58% of patients with abnormal SFEMG in the EDC performed within 4 months of symptom onset developed GMG, whereas 82% of those with a normal study remained with OMG. Rostedt et al. [8] conducted a retrospective analysis of 50 OMG patients who had SFEMG of the EDC 1 month to 11 years after the onset of symptoms and who had received no treatment except cholinesterase inhibitors. Analysis did not demonstrate that the amount of jitter in the EDC muscle predicted the development of generalized MG or that there was a threshold jitter value that predicted development of generalized weakness [8]. Although SFEMG at disease onset does not predict which OMG patient is more likely to develop GMG, normal jitter in the EDC indicates which patients are likely not to progress.

A cooling test for the diagnosis of MG has been shown to be simple, fast, specific, and relatively sensitive in differentiating myasthenic from nonmyasthenic eyelid ptosis. The palpebral fissure increased at least 2 mm in size immediately after application of ice to the ptotic eyelid for 2 minutes in 16 of 20 MG patients, but in none of 20 patients with ptosis not due to MG [9]. This test should be considered as a convenient alternative to the Tensilon test (Roche, Basel, Switzerland) in the clinical evaluation of ocular MG.

Autoantibodies against the muscle nicotinic acetylcholine receptor (AChR) are found in the serum of 80% of patients with generalized MG and in about 50% of patients with OMG. Although their presence confirms the diagnosis, their absence does not rule out MG, and leaves clinicians uncomfortable, especially in atypical cases. Their absence raises questions about the pathogenic mechanism in seronegative patients. A recent study has shown that 70% of AChR-antibody–seronegative MG patients have serum autoantibodies against the muscle-specific receptor tyrosine kinase (MuSK). The MuSK antibodies are not present in AChR-Ab–seropositive MG patients and, therefore, define an immunologically distinct form of the disease [10••]. Measurement of MuSK antibodies is expected to substantially aid in the diagnosis and help guide clinical management of MG in the very near future, and may help elucidate the pathogenic mechanism in seronegative MG patients.

The presence of antistriated muscle antibodies in the serum of MG patients has long been recognized, but their role, if any, in the pathogenesis of MG remains unclear. Titin is the major autoantigen recognized by antistriated muscle antibodies. In the largest study of titin antibodies in MG yet reported, Yamamoto et al. [11] shed some light on the relation between anti-titin antibodies and MG. A highly specific radioligand assay for the MG130 peptide of titin was performed on 398 patients with generalized MG and 237 control patients, including normal elderly individuals and patients with other autoimmune and neurologic diseases [11]. The study showed the following three points: 1) anti-titin antibodies are not present in normal elderly individuals or in patients with other autoimmune or neurologic diseases, and they have a high specificity for MG, comparable with that of AChR antibodies; 2) anti-titin antibodies are a sensitive marker for the presence of thymoma in patients with MG below the age of 60 years, thus their presence justifies a more aggressive search for a thymoma in this age group; and 3) in patients without thymoma, anti-titin antibodies are found almost exclusively in patients with late-onset MG (after 60 years of age).

Based on these observations, the authors wondered whether the presence of a thymoma alters the way titin is presented to T cells and whether late-onset MG with anti-titin Abs represents a subset of patients with a different pathogenic mechanism.

Outcome Measures for Myasthenia Gravis: What We Have and What We Need
Several effective therapeutic options are available for the treatment of MG. However, it is not clear what is the best approach for different subgroups of patients, and clinical practice is currently based more on expert opinion than evidence-based guidelines. This is due, at least in part, to the scarcity of well-controlled treatment trials, but is compounded by the lack of universally accepted classification and grading systems and standardized outcome measures, which makes interpretation of the literature and meaningful comparisons of available data difficult. In an attempt to achieve more uniformity in performing and reporting the results of clinical trials and outcomes research in MG, a Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America (MGFA), formed to develop research standards for MG, recently published the following recommendations [12••].

Clinical trials and reports of treatment in MG should use the following:

1. A standardized clinical classification, the MGFA Clinical Classification.
2. A precise definition of the treatment regimen, using the MGFA Therapy Status.
3. A precise definition of the clinical state after treatment, using the MGFA Post-Intervention Status.
4. A description of the type of thymectomy performed, including details of the surgical technique, grouped according to the primary approach.

The Task Force also recommended that the quantitative MG score for disease severity (QMG), or similar validated strength scoring system, be used in all prospective studies of therapy for MG [13].