Recent Topics in Myasthenia Gravis

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Introduction

Myasthenia gravis (MG), a T-cell-dependent chronic autoimmune disorder, is induced by the sustained production of antibodies that interact with nicotinic acetylcholine receptors (AChR) at the neuromuscular junction.1 MG is characterized by the weakness and the fatigability of skeletal, bulbar and extraocular muscles presenting clinical features in various degrees, such as ptosis, diplopia, dysarthria, dysphagia, dyspnea and muscle weakness of the neck and extremities. This review describes four recent topics in MG: epidemiology, thymectomy, a new subtype of seronegative MG and tacrolimus.

Epidemiology of MG

In Japan, the prevalence of MG increased from 14 per million in 1973 to 89 per million in 1990. Female patients predominate over male patients 2.2 to 1.0. Although MG can develop at any age, the incidence of ocular MG peaks under the age of ten, and two further peaks have been recognized in generalized MG: The peak incidence in females occurs during their thirties and forties and in male patients at middle-age. Recent studies have shown an increased prevalence of MG especially among middle-aged and older patients.2 One study in Nagano Prefecture, Japan revealed that the incidence of MG has increased particularly over the last 20 years, and in the case of elderly-onset MG patients over the age of 65.3 A nation-wide survey of MG patients would serve to clarify the extent of the increased incidence of MG in the elderly population in Japan. The apparent increase in the prevalence of MG both globally and in Japan may be partly due to: 1) the increased accuracy of diagnostic procedures and detection of antibodies that interact with AChR, 2) improved prognosis as a result of managing myasthenic crisis using artificial respirators, which has dramatically decreased mortality, and 3) the advance of the aging society with associated increased life expectancy.

Thymectomy

In 1939, Blalock et al.4 reported the remission of generalized MG after the removal of a cystic thymic tumor. Thymectomy, regardless of the presence of thymoma, has gained widespread acceptance as an early treatment for MG. A recent systematic review of studies describing outcomes in MG patients could not establish the benefit of thymectomy in nonthymomatous autoimmune MG.5 This review concluded that thymectomy is recommended as an option to increase the probability of remission or improvement for patients with nonthymomatous MG. Double-blind studies of thymectomy of MG patients are now being conducted outside Japan and the results are expected within a few years. Recent advances in endoscopic operations include video-assisted thoracoscopic extended...
thymectomy (VATET), which employs extensive removal of the mediastinal thymus and perithymic fat tissue with small operation scars. Outcomes in MG patients undergoing VATET are as favorable as those achieved previously following transternal extended thymectomy.

**Anti-MuSK Antibodies: A New Type of Antibody in Seronegative Patients**

Antibodies that bind to acetylcholine receptors (AChR) are detected in 80 to 90% of MG patients, and these patients have been defined as “seropositive” patients. However, about 15% of generalized MG patients do not have detectable AChR antibodies (seronegative MG). Recently, another type of auto-antibodies against muscle-specific receptor tyrosine kinase (MuSK) was detected in these “seronegative” MG patients. Then, the presence of anti-MuSK antibodies defines a subgroup of 40 to 50% of seronegative MG patients. The percentage of patients with anti-MuSK antibodies in AChR-ab seronegative MG cases is lower in Japan (around 30%) compared to the percentages reported elsewhere. Differences may be due to the race-specific patient profiles. Clinical features of anti-MuSK antibody positive patients are consistent across the countries including Japan. These include female predominance and oculo-bulbar and neck muscle weakness. Wasting of bulbar muscles is evident in some patients with poor response to treatment of these muscles. Other indications include an absence of ocular MG and poor clinical improvement after thymectomy.

Although the pathophysiology of anti-MuSK antibody positive MG has not yet been clarified, morphological damage of motor endplates in these anti-MuSK antibody positive patients was less pronounced than in those with AChR antibodies. The thymus is unlikely to be the main organ of autoimmune reaction in this disease due to the fewer thymic changes in anti-MuSK antibody positive patients than in anti-MuSK antibody negative patients. A lack of improvement of MG symptoms after thymectomy in anti-MuSK antibody positive MG patients also supports the idea that the thymus gland is not implicated in its etiology. This feature of anti-MuSK antibody positive MG patients is quite different from the pathophysiology of seropositive MG, in which thymic abnormalities such as hyperplasia and/or the presence of thymoma are common. In addition, the presence of thymoma was reported in about 20% of seropositive MG patients, but only one patient with thymoma has been reported as an anti-MuSK antibody positive MG case. So far, the thymectomy is not recommended for anti-MuSK antibody positive MG patients without thymoma. For anti-MuSK antibody positive MG patients, treatment with steroids and/or other immunosuppressive drugs has resulted in clinical improvement.

**Tacrolimus Treatment**

The treatment of MG patients includes anticholinesterase agents, thymectomy, immunosuppressive therapy, plasma exchange (plasmapheresis) and intravenous immunoglobulin. However, for these patients, steroids are the first choice of drugs along with various kinds of immunosuppressants, such as azathioprine, cyclophosphamide, cyclosporin and tacrolimus. Of these drugs, only tacrolimus can be prescribed to MG patients under the health insurance in Japan. Tacrolimus, a macrolide immunosuppressant derived from *Streptomyces tsukubaensis* discovered in Japan, possesses strong immunosuppressive effects and specifically inhibits the activation of T-cells. Tacrolimus inhibits the production of a number of cytokines interacting with helper T-cells, and consequently decreases the production of antibodies by B-cells. These immunosuppressive effects are similar to those of cyclosporin which a double-blind study has proved to be effective for the treatment of generalized MG. Tacrolimus shows additional beneficial effects aside from those of cyclosporin. Firstly, tacrolimus increases the concentration of the intracellular calcium level enhancing the functioning of ryanodine receptors, which, in turn, increases the strength of muscle contraction. Secondly, tacrolimus also enhances the transition of steroids into the nucleus, which promotes the pharmacological effects of steroids.

These additional effects of tacrolimus are advantageous in the treatment of steroid-resistant MG in that lower dosages of steroids are required. Open-label studies of low-dose (3 mg/day) tacrolimus for steroid-dependent generalized MG show improvement in about 47% of patients within four months, and a long-term study of more than one year’s treatment...
showed further improvement of MG symptoms. No serious side effects were observed during these studies, but diabetogenic side effects are more likely than nephrotoxic side effects. There are many open-label studies of tacrolimus with progressive reduction of steroids achieving pharmacological remission. Yet, since tacrolimus lacks evidenced-based data, a double-blind study is planned for the near future in Japan.

**Summary**

At present, acquired autoimmune MG can be divided into at least three distinct subtypes according to the presence of auto-antibodies: 1) anti-AChR antibody positive (seropositive MG); 2) anti-MuSK antibody positive (in seronegative MG cases); 3) antibody undetermined. The increased incidence and prevalence, especially in aged populations, will be investigated in Japan in the near future. Evidence-based results will clarify the effects of thymectomy in nonthymomatous MG patients. Until then, experienced clinicians recommend thymectomy during the early stages of disease within one year from the onset of MG symptoms. The pathophysiology of the anti-MuSK antibody will become clear in the near future at which time the production of an autoimmune animal model will also be possible. Tacrolimus, one of the immunosuppressants, improves steroid-resistant MG symptoms with a reduction of steroid dosages.

**References**