

Myasthenia Gravis

What is myasthenia gravis?

Myasthenia gravis is the most common primary disorder of neuromuscular transmission. Literally, the Greek noun "*myasthenia*" means "muscle weakness" and "*gravis*" is Latin for "grave" or "severe". The disease is caused by autoantibodies against the acetylcholine receptor (AChR) in neuromuscular junctions. A normal neuromuscular junction releases acetylcholine (ACh) from the motor nerve terminal. ACh diffuses

across the synaptic cleft and binds to receptors on the muscle end-plate membrane causing muscle contraction.



In myasthenia gravis, the post-synaptic muscle membrane is distorted; the concentration of AChR on the muscle end-plate membrane is reduced, and antibodies are attached to the membrane. ACh is released normally, but its effect on the post-synaptic membrane is decreased. The probability that any nerve impulse will cause a muscle action potential is also reduced, leading to easy fatigue of certain voluntary (skeletal) muscle groups.

The course of the disease is variable but usually progressive. In the era before treatment with corticosteroids became available, approximately one-third of patients improved spontaneously, one-third became worse, and one-third died of the disease. Spontaneous improvement frequently occurs early in the course of the illness. In the other patients, symptoms become progressively severe for several years. After 15 to 20 years, weakness becomes fixed and the most severely involved muscles begin to waste. In extreme cases patients die from a myasthenic crisis characterised by severe generalised weakness and respiratory failure. With current therapies, fortunately, most cases of myasthenia gravis are no longer as "grave" as the name implies. In fact, for the majority of patients, life expectancy is not lessened by the disorder.

Who does myasthenia gravis affect?

Myasthenia gravis occurs in all ethnic groups and both genders, but women are more often affected than men. The most common age at onset is their teens and twenties for women and for men in their sixties and seventies. The disease is not directly inherited nor is it contagious. Occasionally, it may occur in more than one member of the same family. The prevalence of myasthenia gravis in Europe is estimated at 15 per 100,000 of the population, which corresponds to approximately 72,000 cases in the European Union. However, the disease is probably under diagnosed.

Patients with myasthenia gravis complain of specific muscle weakness. Ocular motor disturbances, drooping of one or both eyelids (ptosis) or blurred and double vision

(diplopia), are the initial symptom in two-thirds of patients. Weakness of the muscles of mouth and throat (oropharyngeal muscles), difficulty chewing, swallowing, or talking (dysarthria), is the initial symptom in some 20 per cent, and weakness in arms, hands, fingers, legs, and neck in the other sixth of patients. The severity of weakness fluctuates during the day, usually being least severe in the morning and worse as the day progresses, especially after prolonged use of the affected muscles. Serum antibodies that bind human AChR are found in about 75 per cent of patients with generalized myasthenia and in more than 50 per cent with ocular myasthenia.

Present treatments:

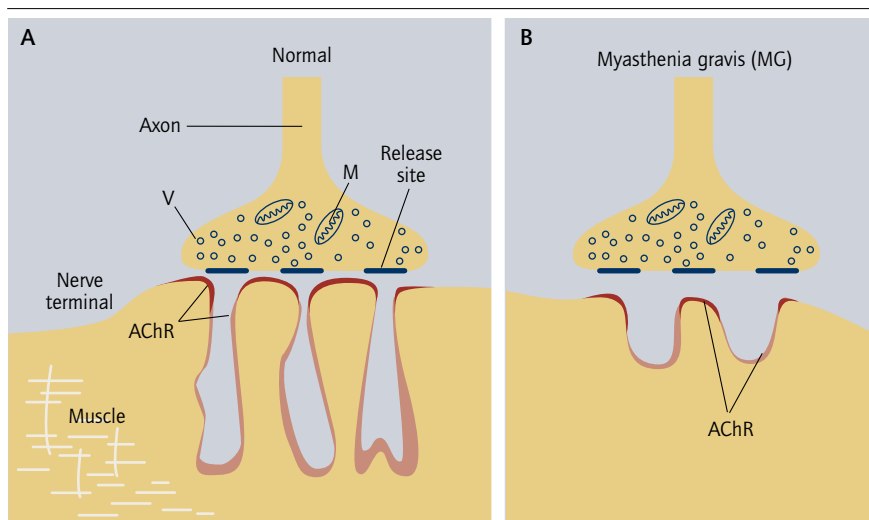
Cholinesterase-inhibitors (ChEIs) retard the enzymatic hydrolysis of ACh at cholinergic synapses. ACh accumulates at the neuromuscular junction and its effect is prolonged. ChEIs cause considerable improvement in some patients and little to none in others. Strength rarely returns to normal. No fixed dosage schedule suits all patients. The need for ChEIs may vary from day to day and during the same day.

Marked improvement or complete relief of symptoms occurs in more than 75 per cent of patients treated with corticosteroids. The best responses occur in patients with recent onset of symptoms, but patients with chronic disease may also respond.

Immunosuppressant medicines reverse symptoms in most patients but the effect is delayed by four to eight months. Once improvement begins, it is maintained for as long as the medication is given, but symptoms recur two to three months after discontinuation of treatment. Immunosuppressants which inhibit predominantly T lymphocyte-dependent immune responses (calcineurin-inhibitor type) are also being used in treating myasthenia gravis. Most patients improve one to two months after start of treatment and improvement is maintained as long as the treatment is continued.

Several groups have reported a favourable response to high-dose treatment with intravenous immunoglobulin. The mechanism of action is not known but is probably non-specific down regulation of the patient's own antibody production.

Myasthenia gravis is a disorder of the junction between the nerves and the skeletal muscles. The result is that muscles get steadily weaker finally leading to respiratory failure. For almost all patients, current therapies mean that myasthenia gravis does neither interfere with their daily activities, nor shorten their life.



Diagrams of (A) normal and (B) myasthenic neuromuscular junctions; V, vesicles; M, mitochondria - the MG junction shows reduced number of AChRs (stippling); flattened, simplified postsynaptic folds; a widened synaptic space; and a normal nerve terminal

Plasma exchange is used as a short-term intervention for patients with sudden worsening of myasthenic symptoms, and as a chronic intermittent treatment for patients who are not responding to all other treatments. The need for plasma exchange and its frequency of use is determined by the clinical response in the individual patient.

Thymectomy is recommended for most patients as thymic abnormalities are clearly associated with myasthenia gravis, but the nature of the association is uncertain. The thymus is the central organ for immunological self-tolerance. In 10 per cent of cases, a thymic tumour is found and in 70 per cent the thymus shows so-called germinal cen-

tres that indicate an active immune response. These are areas within lymphoid tissue where B lymphocytes interact with helper T lymphocytes to produce antibodies. Apparently, thymic abnormalities cause the breakdown in tolerance that induces an immune-mediated self-attack on AChR in myasthenia gravis. The most favourable response to thymectomy generally occurs two to five years after surgery. The best results are seen in young people early in the course of their disease.

What's in the development pipeline?

Research groups are investigating the possibility of treating myasthenia gravis with a medicine originally developed to prevent immune rejection of transplanted organs. Its advantages over other immunosuppressants could be the more rapid onset of effect.

There are about 15 per cent of "seronegative" patients with myasthenia gravis, who have no AChR antibodies detectable in their blood. In some of them, antibodies to MuSK can be shown, a protein that helps organize AChR on the muscle cell surface. It seems that MuSK-positive patients have a distribution of weakness different from that seen in individuals with AChR-positive myasthenia gravis. More remarkably, conventional treatment with ChEIs and thymectomy is ineffective in some of them. Detection of patients with MuSK antibodies might be useful for selecting tailor-made and effective treatments.

A Phase 3 clinical study with a novel immunosuppressant is underway and results are being expected in 2006. Another concept pursues a treatment with an immunosuppressant calcineurin inhibitor, which is already approved for myasthenia gravis in Japan.

In November 2003, an oral antisense product has received US orphan drug status, for the treatment of myasthenia gravis. The compound has been designed to control the production of a stress-response variant of an AChE isoform that is believed to play a key role in the onset and progression of the disease.

The longer-term future:

Much has been learned about the underlying pathological mechanisms of myasthenia gravis during the past 20 years. What was once a relatively obscure condition is now a very well characterised and understood autoimmune disease. The future lies in the elucidation of the molecular immunology of the anti-AChR response.

To this end, several categories of theoretical treatment strategies are actually being pursued: (i) therapies which target the antigen specific B lymphocytes; (ii) therapies which target the antigen specific T lymphocytes; (iii) therapies which interfere with co-stimulatory response for antigen presentation; and (iv) therapies which intervene with the functions of mediating factors (cytokines) and discourage autoimmune inflammatory responses.



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