



Treatment of myasthenia gravis

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Summary

Myasthenia gravis is a syndrome of weakness and fatigue due to dysfunction of the neuromuscular junction. It is an antibody-mediated autoimmune condition with a range of moderately effective treatments. Occasionally patients go into remission spontaneously, but most require treatment. Mild disease, such as that confined to the ocular muscles, can often be treated with pyridostigmine alone. More significant or generalised weakness requires immunosuppression, principally with prednisone and azathioprine. The response to immunosuppression is slow, ranging from several months to 1–2 years for a full response. Short-term use of antibody-based therapy such as plasma exchange or intravenous immunoglobulin is warranted for more severely affected patients. Thymectomy offers the hope of drug-free remission but as yet remains unproven. Treatment-related morbidity is considerable, but partly preventable.

Key words: azathioprine, immunosuppression, prednisone, pyridostigmine, thymectomy.

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Introduction

Myasthenia gravis is an autoimmune disease which causes muscular weakness due to dysfunction of the neuromuscular junction (Fig. 1). Autoantibodies directed against antigenic proteins on the postsynaptic side of the neuromuscular junction result in both blockade of transmission and damage to the postsynaptic structure. As a result the motor neuron is unable to 'talk' to the muscle fibre and weakness results. The known antigens to which the autoantibodies bind are the acetylcholine receptor and, less commonly, muscle-specific tyrosine kinase.

The prevalence of myasthenia gravis is about 1 in 10 000. The gender ratio is approximately equal, with a peak incidence of onset in the 20s for women and the 60s for men. Around 10% of patients with a positive acetylcholine receptor antibody test have an associated thymoma.

Diagnosis

There are a range of diagnostic tests for myasthenia gravis. These include dynamic tests for measuring muscle weakness (for example, response to edrophonium or ice pack), electrical tests such as repetitive stimulation or single fibre electromyography, and measurement of antibodies to acetylcholine receptor and to muscle-specific tyrosine kinase.

Clinical manifestations

Myasthenia gravis affects some regional muscles more than others. Most commonly the orbital muscles are affected first, with either diplopia or ptosis. However, myasthenia gravis may first affect the bulbar muscles (speech and swallowing), the neck muscles (head drops) and proximal or rarely distal limb or respiratory muscles. Involvement is fairly symmetrical except in the eyes. Symptoms may get worse towards the end of the day or after a few minutes of continuous use – for instance speech may become slurred over a few minutes. More severe myasthenia gravis affects multiple muscular regions and may be sufficiently severe to cause respiratory failure and death if untreated.

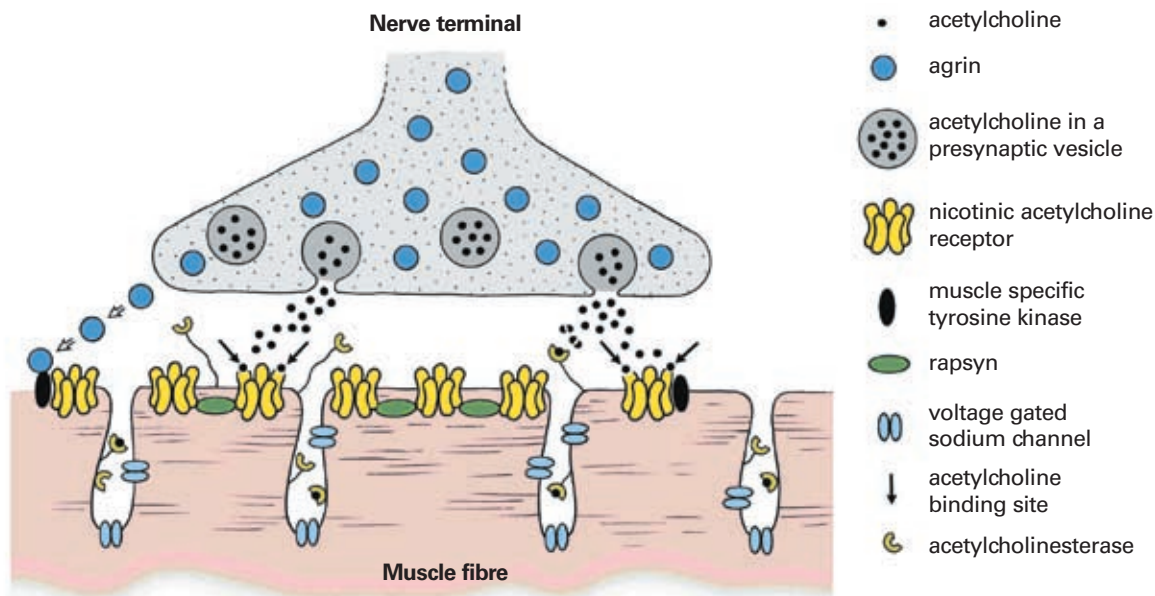
Natural history of myasthenia gravis

Generally, myasthenia gravis is a persistent disease requiring chronic treatment. Fluctuations over the long term are the norm. Some patients go into long-term remission spontaneously – approximately 15–25% after five years for those presenting with generalised disease and somewhat more for those presenting with ocular disease only. Late relapse after sustained remission also occurs, the longest reported example being after 32 years. It should be noted that the neuromuscular junction can be reformed, unlike many parts of the nervous system. Muscle strength that has been affected by myasthenia gravis for a long time often recovers with treatment. This means that the intensity of treatment for myasthenia gravis can be modulated to the current severity of the disease.

Over time, patients with clinically isolated ocular myasthenia gravis often progress to generalised myasthenia gravis. Treatment with corticosteroids can reduce the likelihood of progression, and control both ocular and generalised weakness completely in many cases. It is not known if this alters the natural history or the need for long-term treatment. It is therefore unclear whether treatment should be commenced for ocular disease or just 'as required' to control symptoms that

Fig. 1

Normal muscular junction



In the normal neuromuscular junction, acetylcholine released from the nerve terminal following a nerve action potential, binds to the acetylcholine receptor on the postsynaptic muscle, triggering a muscle action potential propagated by the voltage gated sodium channel. Acetylcholinesterase scavenges and breaks down unbound acetylcholine. In a separate pathway, neural agrin binds muscle specific tyrosine kinase initiating clustering of phosphorylated rapsyn and acetylcholine receptors, stabilising the postsynaptic structure opposite the nerve.

In myasthenia gravis caused by antibodies to the acetylcholine receptor, there is blockade of the binding site for acetylcholine, cross-linking of the acetylcholine receptor with subsequent internalisation and reduction in its surface expression, and initiation of complement and cellular inflammatory cascades with damage to the post- and presynaptic structures. The molecular physiology of myasthenia gravis mediated by antibodies to muscle specific tyrosine kinase has not been established.

are causing sufficient disability to justify the adverse effects of treatment. Long-standing ocular misalignment may not recover despite generalised remission.

Treatment

The diagnosis must be confirmed before treatment, because the mainstay of treatment for most patients is immunosuppression. Treatments to prevent the adverse effects of immunosuppression should be started simultaneously with the therapy (see Table 1). There is no robust evidence that long-term treatment actually cures the condition, so some patients choose to avoid the adverse effects of immunosuppressive therapy and accept degrees of weakness. Coping without treatment is not always the safest strategy as patients with significant weakness, particularly in the bulbar musculature, are at risk of ventilatory failure or of needing intensive care following an intercurrent respiratory infection. Immunosuppressive treatment is therefore strongly recommended for control of significant bulbar weakness.

Initial treatment is usually with pyridostigmine, followed by prednisone and azathioprine if the response is incomplete. A combination of approaches is often useful to cover deficiencies in each available drug.

Immunosuppression produces a very slow response, often taking many months to 1–2 years.^{1,2} An unrealistic expectation of a speedy response is often a problem for both the patient and the doctor.

There are four main approaches to treatment, each with very different durations of effect, requirements, consequences and adverse effects.

Improve neuromuscular transmission by inhibiting acetylcholinesterase

Drugs that inhibit acetylcholinesterase include pyridostigmine, edrophonium (used only for testing) and neostigmine (for intravenous use in intensive care units only). These drugs take effect within minutes and last for hours. Although they are without long-term adverse effects, the efficacy of all

Table 1

Prophylaxis of the complications of immunosuppression

Osteoporosis prevention	Measure bone density before treatment and yearly while on treatment. Start calcium and vitamin D supplements. Bisphosphonates may reduce bone loss associated with the chronic use of glucocorticoids.
Cardiovascular risk	Risk factor modification should be standard and includes advice to stop smoking, start an exercise program and manage hypertension.
Peptic ulcer prevention	Helicobacter screening and prophylactic treatment with proton pump inhibitors or H ₂ antagonists seems appropriate for those with a past history of previous ulceration or concordant use of non-steroidal anti-inflammatory drugs.
Infection prophylaxis	Use of inactivated vaccines such as influenza is recommended. Live vaccines are contraindicated. A chest X-ray should be performed prior to treatment. More specific testing for tuberculosis may be indicated depending on history and chest X-ray results.
Malignancy prevention	Skin cancer rates are increased in patients using azathioprine. A full yearly dermatological survey is recommended. Exhort sun protection and cancer surveillance. Regular cervical smears are recommended. Eye protection may also limit cataract development.

acetylcholinesterase inhibitors is limited. As a sole drug they are not enough for most patients with generalised myasthenia gravis.

Pyridostigmine

Pyridostigmine is the first-line treatment for myasthenia gravis. It is a reversible inhibitor of acetylcholinesterase so increases acetylcholine stimulation of the remaining acetylcholine receptors. If there are insufficient acetylcholine receptors remaining to trigger a muscle action potential, extra acetylcholine from the action of the drug is not going to help. The underlying autoimmune state is not altered. It is often sufficient for ptosis alone, but not for diplopia or generalised myasthenia gravis. Benefit is often not sustained, possibly due to counterproductive upregulation of acetylcholinesterase and downregulation of acetylcholine receptors. The dose required is variable, as is gastrointestinal tolerance. One approach is to start at 10 mg three times a day and titrate up to 60 mg 4–6 times daily. A 180 mg 'timespan' preparation is available for nocturnal symptoms. In practice a degree of patient control of dosing and 'when required' use is often helpful.

Doses less than 480 mg daily rarely produce depolarising crisis. Increasing weakness after an increase in the pyridostigmine dose (when high doses are already being given) suggests deteriorating disease and/or a depolarising crisis. This may require treatments such as plasma exchange and a reduction in pyridostigmine dose. The presence of gastrointestinal adverse effects and fasciculations, clinically or on electromyogram, might suggest depolarising crisis. The patient must be hospitalised and the dose of pyridostigmine reduced while they are carefully monitored. Lack of improvement with edrophonium (which has a very short half-life) indicates that further pyridostigmine will not be useful.

Immunosuppression

The principal drugs used to suppress the immune system in myasthenia gravis are prednisone (a glucocorticoid) and azathioprine. The response to these treatments can take weeks to many months, with the maximal effect taking months to years.^{1,2}

Prednisone

Prednisone or another corticosteroid is the primary immunosuppressant used in myasthenia gravis. Sustained improvement or remission can be achieved while patients remain on treatment. A typical course for generalised myasthenia gravis would use 1 mg/kg prednisone daily (0.5 mg/kg for ocular myasthenia gravis) until clinical control is achieved and then weaning either directly or by initial conversion to alternate daily dosage, with the determination of a maintenance dose by trial and error during a slow withdrawal of medication over many months. Deterioration in myasthenia gravis can occur in the first few weeks of treatment so the dose is often increased slowly. The mean time to maximal effect of prednisone in myasthenia gravis is six months – much longer than most expect.

Azathioprine

Azathioprine is used as a steroid sparing drug and additional immunosuppressant with prednisone. In a randomised trial, after three years of treatment, 63% of patients with myasthenia gravis taking azathioprine were off all prednisone, versus 20% taking placebo, but no effect was seen in the first year.² Compared to the metabolic consequences of continued corticosteroids, the problems of azathioprine seem significantly less. However, the long-term consequences do include an increased risk of skin cancers and a small possible increase in the risk of haematological malignancies. About one-fifth

of patients cannot take azathioprine due to rash, hepatitis, myelosuppression, nausea or vomiting, but this is usually evident within two weeks to two months. Some doctors routinely use azathioprine for patients with generalised myasthenia gravis still requiring more than 10 mg prednisone per day at six months, or if severe disease is obvious earlier.

Other drugs

If not using azathioprine, other steroid-sparing drugs used include mycophenolate mofetil, cyclosporin, methotrexate and cyclophosphamide. Experience with these drugs is generally derived from retrospective series. None of these have proven efficacy in randomised trials except for cyclophosphamide, and choice of drug depends on age and competency of the patient plus local experience of the physician. In practice they are frequently used with apparent success, but like azathioprine the response is often slow.

Mycophenolate mofetil is a pharmacologically similar alternative to azathioprine but two recent randomised controlled trials failed to demonstrate benefit in myasthenia gravis.* The duration of both trials was less than a year. As it works in the same pathway as azathioprine this may have been inadequate and it remains widely used.

Rituximab, a monoclonal antibody specific to CD20 (on B cells), or bone marrow ablation with autologous transplant are treatments of last resort.

Remove or block autoantibodies

Plasma exchange removes autoantibodies and intravenous immunoglobulin is thought to block autoantibodies. These treatments take effect within days, but only last weeks before treatment needs to be repeated. They have a key role in stabilising severe myasthenia gravis and in preparation for surgery, or in pregnancy.

Plasma exchange is expensive and only available in major hospitals. It requires good intravenous or alternatively central catheter access, but a central line increases the risk of infection. Intravenous immunoglobulin, a purified blood product, is also very expensive and is in limited supply. Its mode of action remains unclear.

Thymectomy

Thymectomy has a possible immunomodulatory role in the absence of thymoma. Results of a global randomised trial are awaited.† The effect of a thymectomy appears to take years. Non-randomised retrospective data suggest there is an increased complete remission rate from thymectomy when it is performed within 2–3 years of the onset of disease. This

treatment involves major surgery with midline sternotomy, although minimally invasive approaches are becoming available. Other than surgical complications there are no known long-term adverse effects.

Thymectomy for thymoma does not on average improve myasthenia gravis, but is required to remove the tumour.

Drugs that worsen myasthenia gravis

Neuromuscular blocking drugs used for intubation and muscle relaxation in surgery cause profound deterioration in myasthenia gravis with marked prolongation and severity of neuromuscular dysfunction. The diagnosis of myasthenia gravis should be considered if patients fail to breathe spontaneously or are weak after an anaesthetic.

Aminoglycosides such as gentamicin partially block the neuromuscular junction and dramatically worsen myasthenia gravis. Beta blockers have a generally mild adverse effect (adrenergic stimulus is mildly beneficial for myasthenia gravis) and the need to use them should be carefully considered. Anticholinergics of all types logically have a deleterious effect on the neuromuscular junction. In practice a muscarinic anticholinergic such as propantheline is sometimes used to control the adverse effects of pyridostigmine on the gut. Many other drugs have been cited as provoking deterioration in myasthenia gravis or have myasthenia gravis listed as a contraindication to use in the product information. This includes tetracyclines and quinolones, which in practice are only occasionally problematic. Sedatives such as narcotics and benzodiazepines have no direct effect on the neuromuscular junction but obviously are contraindicated if hypercapnia or respiratory failure are a risk.

Conclusion

Myasthenia gravis is a readily treatable condition and many patients can expect to have little disability. It should be acknowledged that of the residual disability, a considerable amount comes from the treatment. Attempts to re-establish immune tolerance of the acetylcholine receptor to cure the condition have not yet borne fruit. No revolution in treatment is expected in the near future.

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Further reading

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Stephen Reddel is an investigator of the United States National Institutes of Health (NIH) randomised clinical thymectomy trial currently underway. The NIH has paid for a trial workshop including travel. He has also received a consultancy fee from

Aspreva, marketing company of mycophenolate mofetil for use in autoimmune diseases.

Self-test questions

The following statements are either true or false (answers on page 167)

- In patients with myasthenia gravis, the maximum response to therapy is seen within six months of starting azathioprine.
- Myasthenia gravis may be exacerbated when a patient starts prednisone.

Dental notes

Prepared by Dr M McCullough of the Australian Dental Association

Treatment of myasthenia gravis

The prevalence of myasthenia gravis (about 1 in 10 000 people) is such that every dentist will probably treat more than one patient with the condition during their career. Changes in tongue and facial muscle strength can often be the first sign of myasthenia gravis. These changes may impact on oral hygiene and the ability to wear dentures. Postural changes and the potential for the patient's medication to interact with drugs given by the dentist means that patients with myasthenia gravis have specific needs during dental treatment.

A review of the dental literature recommended that, depending on the severity of disease, patients should have multiple, short, early morning appointments, perhaps preceded by oral anticholinesterase drugs, to take advantage of their early

morning muscle strength.¹ Factors related to dental treatment that are likely to worsen myasthenia gravis should be avoided, such as stressful protracted procedures, the use of ester-linked local anaesthetics (not available in Australia) and the use of antibiotics that have some muscle relaxing properties (erythromycin, gentamicin, neomycin and clindamycin).¹ The use of these drugs, as well as the use of benzodiazepines, sedation and general anaesthesia, has been reported to worsen muscle weakness and should only be undertaken after consultation with the patient's physician. To avoid complications, dentists should therefore have good communication not only with the patient, but also with the treating physician.

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Patient support organisation

Australian Myasthenic Association in NSW

The Australian Myasthenic Association in NSW was set up to support sufferers of myasthenia gravis and their carers. It has members from all over Australia and overseas.

The website contains useful information about myasthenia gravis, its causes, symptoms, diagnosis, treatments and history. There are links to a range of patient support resources such as newsletters, chat facilities, events, patient experiences and

practical lifestyle advice. A membership fee entitles members to receive the association's newsletters and goes towards funding events and other costs.

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