

Diagnosis and Management of Myasthenia Gravis

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Abstract

Myasthenia gravis was first described 300 years ago,¹ but today is one of the most well characterised autoimmune diseases. Whilst its prognosis was previously grave, cholinergic and immunomodulatory therapy has greatly improved survival over the last two decades. Improved recognition of the condition and effective therapy has transformed this previously debilitating and often fatal condition into an eminently treatable and reversible condition.

Keywords

Myasthenia gravis, Tensilon test, anti-acetylcholine receptor antibodies, steroids.

Introduction

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction resulting in fluctuating weakness and fatigue. MG is antibody-mediated and in 85% of patients autoantibodies to the nicotinic acetylcholine receptor (AChR) are present; antibodies targeted against other proteins of the neuromuscular junction are probably responsible for the remainder.

The annual incidence is between 0.25 and 2.0 cases per 100 000, with a recently reported prevalence of 15/100 000 in the UK.² Increased recognition of the condition, improved survival and greater longevity of the population are likely to increase prevalence rates further in the future. The disease may occur at any age although onset in the first decade is rare. The peak age of onset tends to be between the 3rd and 4th decades in women and the 6th and 7th decades in men. In patients less than 40, women are affected more than men (ratio female: male 2:1); however, in later years there is more of a bias towards men. It is important to remember that MG is not merely a disease of the young and is being increasingly recognised in older people.^{3,4,5}

The most important association of MG is with thymic tumours and approximately 10% of patients with MG have a thymoma. MG can also be induced by penicillamine treatment, although this form of the disease tends to remit on withdrawal of the drug. Presentation or exacerbation of MG can also be precipitated by systemic illness, pregnancy, menstruation, endocrine disturbance and drugs, especially aminoglycosides.

Key Points

1. Myasthenia gravis is an uncommon autoimmune condition affecting 15/100,000 people in the UK.
2. Clinical presentation is with muscle weakness and fatigue, which may be generalised or cause diplopia, ptosis or dysarthria.
3. Investigations should include a Tensilon test, Acetylcholine receptor antibody measurement and electrophysiological testing.
4. Treatment is with anticholinesterase and corticosteroid drugs; plasma exchange or immunoglobulin may be required.

Making the diagnosis

The history and examination are the most important clues to the diagnosis and a high index of suspicion is required, particularly in the elderly where it is often misdiagnosed as a stroke or motor neurone disease. Once suspected, three main investigations are used to confirm the diagnosis: the Tensilon test, measurement of the anti-AChR antibody titre and electrophysiological tests. However if the patient is unwell treatment should not be deferred whilst awaiting the results of detailed investigations and specialist neurological advice should be sought as soon as possible. It is important to reach a firm diagnosis in the long term, as it is likely to commit patients to prolonged therapy with drugs that may cause significant side effects.

Clinical Presentation.

The onset of MG is highly variable; in some there is a sudden, onset deteriorating over days, while in others, onset it is more insidious, developing over months or years.

The most characteristic presentation of MG is painless, fatiguable weakness, increasing with activity and alleviated by rest. Ptosis and ophthalmoplegia are the presenting feature in about half the cases eventually affecting over 90%. Ptosis can often be induced by asking the patient to look up for about a minute. In 15% of people, MG remains confined to the ocular muscles, the so-called "ocular myasthenia".⁶ Ocular palsies and ptosis are often accompanied by weakness of eye closure (this combination only occurs in MG and muscular dystrophies). Ocular palsy does not usually correspond to a particular cranial nerve innervation

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and tends to fatigue with repeated eye movement. Weakness of the facial, masticatory and bulbar muscles occurs in 80% of patients, but is the presenting feature in only 5-10%. The smile may appear flattened or transformed into a snarl. The speech may be nasal and quiet and tends to fatigue on prolonged conversation. The patient may report difficulty in chewing or swallowing, particularly at the end of a meal and modifications to their diet may be apparent from the history. Palatal weakness may result in fluids escaping from the nose during drinking. The patient's ability to cough may also be compromised, which combined with bulbar weakness makes them at risk of aspiration. Jaw weakness may cause the jaw to drop open and weakness of the erector spinae muscles may cause the head to droop forwards.

Generalised weakness occurs in approximately 85% of patients and can affect the diaphragm and intercostal muscles. This may lead to respiratory compromise, especially on lying flat. If the trunk and limbs are affected, proximal muscles tend to be affected more than distal muscles. Asking the patient to repeatedly lift one arm above their head and then comparing power with the unexercised side can demonstrate fatigable weakness of shoulder abduction. Tendon reflexes are unaffected and weak muscles undergo only minimal atrophy. Sensory findings are absent and smooth and cardiac muscles are not involved.

Edrophonium (Tensilon) test: (Figure 1)

The Tensilon (edrophonium, Cambridge Laboratories, Tyne & Wear) test relies on a visible improvement in muscle weakness in response to the administration of a short-acting anticholinesterase. It is important to select a clear and objective measure of improvement, for example, elevation of a ptosed eye-lid or clarity of speech when counting. A video of the test can be very helpful. Some clinicians perform the Tensilon test in a double-blinded fashion, comparing the patient's response to Tensilon to that of normal saline. However the side effects of Tensilon, (salivation, myokymia and mild bradycardia) generally make it clear to the experienced observer which drug has been administered. Furthermore the effect of Tensilon may exceed 5 minutes, making it difficult to follow Tensilon with saline. It is therefore better either to perform the test in a single blind fashion (telling the patient that one of the administered drugs may work and starting with the normal saline) or to accept that there may be a placebo response and only use Tensilon.

A variety of complications of the Tensilon test have been reported, including bradyarrhythmias, respiratory arrest, seizures, severe vomiting and transient ischaemic attacks.^{7,8} Although pre-treatment with atropine negates some of the muscarinic effects of Tensilon, it is important that all tests are performed in an environment with full resuscitation facilities and where the patient can be monitored for at least thirty minutes. A Tensilon test is inadvisable for patients with significant cardiac or respiratory disease, or with severe brittle MG.

Unfortunately, the Tensilon test is not 100% sensitive or specific. A negative test does not exclude MG. False

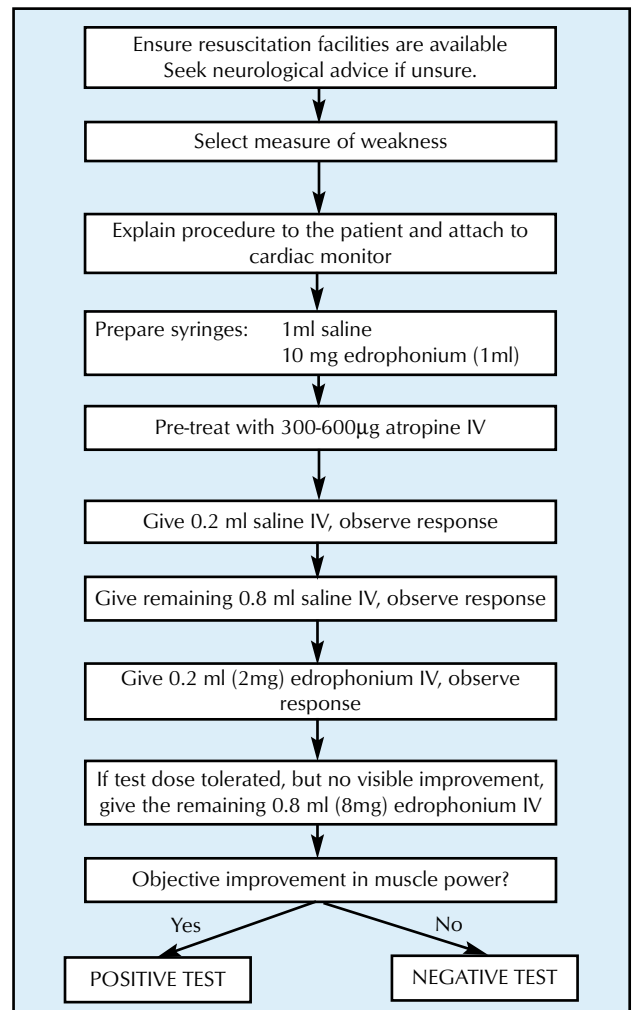


Figure 1. Performing a Tensilon test (single-blinded method).

positives or equivocal results may arise in Lambert-Eaton myasthenic syndrome⁹ thyroid eye disease, Guillain-Barré syndrome,¹⁰ progressive supranuclear palsy, motor neurone disease,¹¹ ocular palsies due to tumours and carotid aneurysms (pseudo-ocular MG).

Antibody estimation

The finding of a positive titre of anti-AChR antibodies is a very specific test for MG; false positives are extremely rare. A negative antibody test does not rule out MG; antibodies are only detected in 55% of ocular myasthenics and approximately 15% of patients with generalised MG are anti-AChR negative. Antibodies targeted against another protein expressed at the neuromuscular junction called Muscle Specific Kinase (MuSK) have been recently discovered in a cohort of 'sero-negative' patients and it is probable that these are responsible for disease pathogenesis.¹² Commercial testing for this antibody is not yet available.

Neurophysiological tests.

Two neurophysiological tests are generally used to demonstrate a defect in neuromuscular transmission in diseases such as MG: repetitive nerve stimulation (RNS) and single fibre electromyography (SFEMG). RNS relies

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on the demonstration of a progressive decline in the compound motor action potential recorded from muscle with repetitive stimulation of the relevant nerve – the neurophysiological correlate of 'fatigue'. This decremental response is seen more often in proximal muscles than distal and false negatives may occur, particularly in mild or ocular disease, if anticholinergics have been given or if the limb is cold.

SFEMG is a more sensitive method of detecting neuromuscular dysfunction. It demonstrates increased variability of the interpotential interval ("jitter") of successive discharges from single muscle fibres belonging to the same motor unit. It is an extremely sensitive test for MG and is reported to be positive in 92% of cases.¹³ However, it is very user dependent and results are most reliable when performed by a neurophysiologist who does the test on a regular basis. Furthermore, many patients find it uncomfortable, particularly when recording from the obicularis oculi. It should be remembered that both RNS and SFEMG are designed to detect defects in neuromuscular transmission and therefore are not completely specific for MG.

Other investigations.

MG is often associated with thymic abnormalities. Anti-AChR antibody positive patients with disease onset under the age of 40 generally have a hyperplastic thymus, removal of which may result in disease remission.^{14,15} Approximately 10% of sero-positive patients have an underlying thymoma, which may invade local structures such as pleura or pericardium. Computed tomography (CT) of the thorax is therefore mandatory in all anti-AChR positive patients presenting *de novo*. Thyroid function should also be checked, as autoimmune thyroid disease often co-exists and dysfunction may contribute to muscle weakness.

Treatment.

The management of a patient presenting with newly diagnosed MG and one with established disease in the throes of a relapse is essentially the same, although in established patients an underlying cause for the exacerbation should be sought. Relapses are commonly triggered by intercurrent infection, though other possible causes are poor tablet compliance, recent surgery, metabolic disturbances (particularly deranged potassium or phosphate levels), or the recent introduction of a drug which exacerbates MG (see Table 1).

Supportive Care

All myasthenics with rapidly deteriorating symptoms should be admitted immediately for observation. Initial assessment in A&E should focus on the adequacy of ventilation and the need for intubation, and the safety of the patient's swallow. Respiratory failure and dysphagia are termed 'myasthenic crisis'. The respiratory rate should be assessed and the presence of paradoxical respiration (spontaneous inward movement of the diaphragm on inspiration) noted. Respiratory reserve can be assessed

•	Penicillamine (absolutely contra-indicated)
•	Antibiotics:
	Aminoglycosides (e.g. gentamicin)
	Erythromycin
	Clindamycin
	Ampicillin
	Ciprofloxacin
	Tetracyclines
•	Anti-arrhythmics:
	Quinidine
	Procainamide
	Lignocaine
•	Quinine
•	Beta-blockers
	Propranolol
	Timolol eye drops
•	Phenytoin
•	Neuromuscular junction blockers
•	Calcium channel blockers
•	Magnesium salts (including laxatives and antacids)

Table 1. Drugs that may exacerbate MG.

quickly by asking the patient to count from 1-25 slowly out loud in a single breath and by measuring the forced vital capacity (FVC), though bulbar or facial weakness may make this unreliable. The strength of the patient's voice and cough gives an indication of bulbar weakness. A gurgling voice and pooled secretions are good indicators of significant dysphagia. If there is any doubt about the safety of the patient's swallow, a nasogastric tube should be inserted and oral feeding stopped. Aspiration is a common cause of respiratory failure in myasthenic crisis.

If the patient is not deemed to require immediate respiratory support, they should be admitted and **closely monitored** with four hourly measurements of vital capacity (VC) and respiratory rate (more frequent if deteriorating). Peak expiratory flow rate is not an adequate substitute for VC and arterial blood gases are not sensitive enough to detect early problems. The patient should be nursed upright or semi-recumbent to prevent aspiration and assessed by a speech and language therapist and dietician as soon as possible. In patients who are immobile, thromboprophylaxis should be considered.

Intubation is indicated if the FVC falls to 15ml/kg (normal is 60-50 ml/kg), if the FVC is declining rapidly or if the patient is getting distressed or excessively fatigued. One advantage of early intubation is that positive pressure ventilation can prevent further atelectasis resulting in earlier extubation. The average duration of respiratory support is two weeks¹⁶ therefore most patients will require a tracheostomy. This has the advantage of increased comfort, reduced risk of tracheolaryngeal injury, improved ability to suction secretions and increased ease of weaning from the ventilator. This is especially important in MG as respiratory muscle fatigue often means that patients can only manage short periods off respiratory support in the early stages of weaning.

Drug treatment

Oral anticholinesterases

Anticholinesterases inhibit the enzymatic hydrolysis of ACh at cholinergic synapses, so that ACh accumulates at the neuromuscular junction and its effect is prolonged. Pyridostigmine bromide (Mestinon) is usually the first

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line agent and is preferred to neostigmine due to its lower incidence of gastrointestinal side effects. Neostigmine has the advantage that it can be given subcutaneously (1–2.5mg every 2–4 hours) and therefore can be used if the patient has severe dysphagia. Side effects such as abdominal cramping and diarrhoea generally respond to muscarinic anti-cholinergic agents such as propantheline and atropine. The initial oral dose of pyridostigmine in adults is 30–60mg every 4–8 hours. High concentrations of anticholinesterases can precipitate increased weakness (cholinergic crisis), therefore doses should not exceed 450mg/day.¹⁷ Patients not adequately controlled on anticholinesterases alone should be started on immunosuppressive treatment rather than continuing to increase the dose of the anticholinesterase. All but the mildest cases will require some form of immunosuppression to keep their symptoms under control.

Corticosteroids

Steroids induce disease remission or produce improvement in over 95% of patients.¹⁸ Instituting therapy or making a significant dose increase can result in an initial exacerbation of weakness. Therefore this should always be done in hospital with careful monitoring. A tapered increase in steroid dose may reduce the incidence of exacerbations.¹⁹ Osteoporosis prophylaxis should be prescribed and gastro-protection considered. A prednisolone dose of 1mg/kg/day should be maintained until the myasthenic symptoms remit, then alternate day doses should be tapered gradually. If the patient is sufficiently unwell to require ventilatory support, they should be commenced immediately on an initial dose of 1mg/kg/day.

Intravenous pooled immunoglobulin and plasma exchange

It may take some weeks before steroids induce disease remission, during which time the patient may continue to deteriorate or require prolonged respiratory support. In such situations plasma exchange or intravenous immunoglobulin (IVIg; 0.4 mg/kg/day for five days) have been shown to be of benefit.^{20,21} Although published reports suggest that the efficacy of the two treatments is comparable,²² anecdotally more patients appear to respond to plasma exchange and the benefit is seen more quickly. However, IVIg is easier to administer and not all hospitals have access to a plasma exchange service. The cost of the two treatments in the United Kingdom is broadly similar. Guidelines for administering IVIg are given in Figure 2. Plasma exchange should be avoided in patients with hypotension, active infection or significant anaemia. ACE inhibitors should be stopped at least 24 hours before the procedure, as they are associated with increased risk of atypical reactions and anaphylaxis during the procedure.²³

Steroid-sparing agents and thymectomy

Once the patient is stable and entering remission, addition of another immunosuppressant should be considered. Azathioprine is the only drug which has been

demonstrated to be of benefit in a randomised controlled trial.²⁴

If the patient has been shown to have a thymoma, they should be referred for excision of the tumour. This does not induce disease remission but removes a possibly malignant tumour from the chest cavity. Conversely, removal of a hyperplastic thymus may result in disease remission and therefore should be performed before additional immunosuppressant agents are considered. Ideally, removal of a hyperplastic thymus should take place before the patient starts steroid treatment though clearly this will depend on their clinical state.

Obtaining consent

IVIg is not licensed for use in myasthenia and adverse effects are common (see below). It is therefore advised that its use is discussed with the patient and where possible informed consent obtained (a patient information sheet and consent form can be found at www.theabn.org/download/IVIgGuidelines).

Administering infusion

1. Check renal and hepatic function and full blood count before administering infusion. If repeated infusions are likely it is reasonable to measure IgA levels as total IgA deficiency is associated with severe anaphylactic reactions with subsequent infusions.
2. Exercise caution and seek advice if patient has impaired renal function, hyperviscosity syndrome, cardiac failure or ischaemic heart disease.
3. Calculate dose on basis of 0.4 g/kg a day for five days.²⁵ Shorter courses with a total dose of 2 mg/kg may be given if well tolerated.
4. Reconstitute according to the manufacturer's guidelines. Solutions should be administered within 6 hours of constitution.
5. A reasonable administration rate is 60 ml/hr for 15 minutes, increasing to 90 ml/hr, 120 ml/hr and 150 ml /hour every 15 minutes if tolerated.
6. Vital signs including temperature should be recorded every 15 minutes during the infusion.
7. If the patient develops a mild reaction to the infusion it should be slowed down and closely monitored. Administration of 1g p.o. paracetamol, 100 mg IV hydrocortisone and / or antihistamines may relieve the symptoms.
8. If the patient develops a severe reaction the infusion should be stopped. Expert advice should be sought before restarting the IVIg and if possible an alternative therapy considered.
9. After the infusion renal function should be monitored.

Adverse Reactions Associated with IVIg Use

Mild reactions such as headache, nausea, shaking, fever and chest tightness are common. More severe reactions included aseptic meningitis, arthritis, acute renal failure, myocardial infarction and anaphylaxis are rare but potentially life threatening. All preparations are screened for HIV and Hepatitis A, B and C. Plasma from the UK is not currently used for the preparation IVIg because of the theoretical risk of variant Creutzfeld-Jakob Disease.²⁶ However it is important to realise that there are no tests for prion disease and it cannot be completely guaranteed that IVIg preparations are free from transmissible pathogens.

Figure 2. Guidelines for Use of IVIg in Myasthenic Crisis.

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