



History central to diagnosing myasthenia gravis

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History central to diagnosing myasthenia gravis

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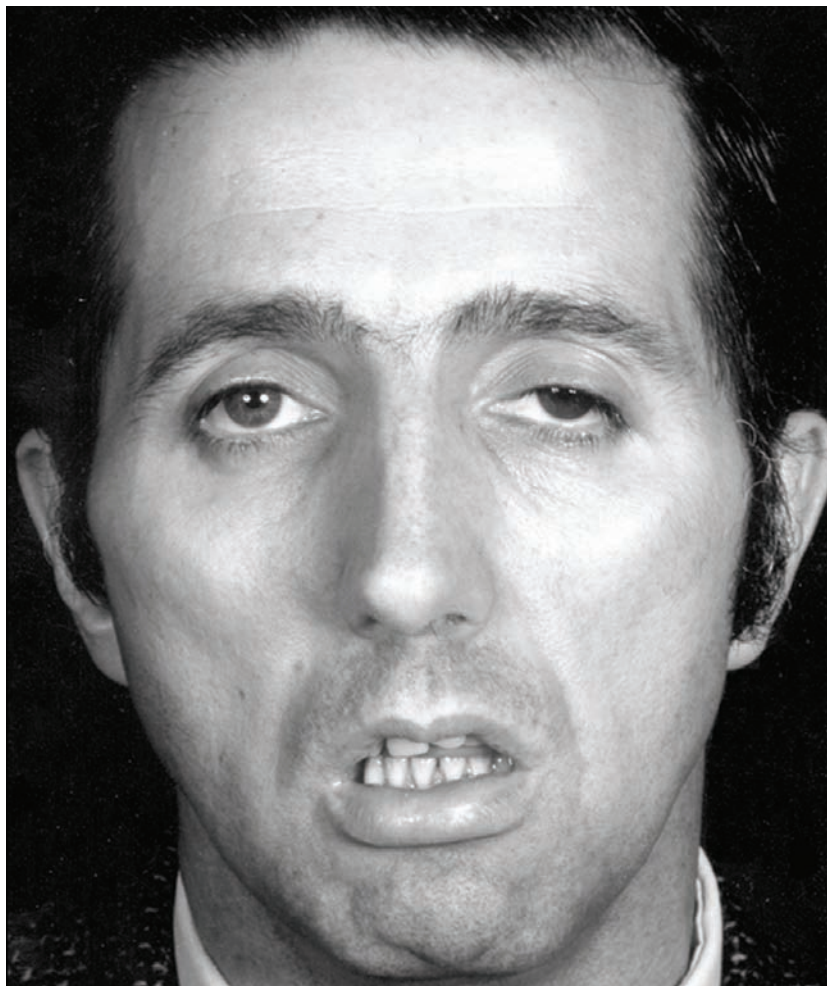
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How does myasthenia gravis present?

What diagnostic tests should be performed?

What are the treatment options?



MYASTHENIA GRAVIS (MG) IS APTLY NAMED. IT MANIFESTS AS GRAVE MUSCLE WEAKNESS THAT

can significantly impact on quality of life and is sometimes fatal. It is caused by failure of chemical transmission at the neuromuscular junction.

MG has a prevalence of around 20 per 100,000, so an average practice may expect to have only one patient.¹ It is important not to miss the diagnosis because the condition is eminently treatable. The incidence is bimodal with a 2:1 female to male ratio in the younger population and a reversed sex ratio over the age of 60.

The reported incidence has been increasing since the mid-1980s, mainly because of increased recognition of late-onset disease.^{2,3}

However, the condition is probably still underrecognised in the very elderly and may be mistaken for other disorders such as stroke, motor neurone disease or Parkinson's disease.

PATHOGENESIS

MG is an autoimmune disorder in which antibodies interfere with neuromuscular transmission.⁴ Circulating antibodies to acetylcholine receptors (AChRs) can be detected

in approximately 85% of patients. In the remaining cases, some have antibodies that recognise muscle-specific kinase (MuSK), which is involved in the clustering of AChRs at the neuromuscular junction, and a small number of patients are persistently seronegative.^{5,6}

In addition, very rare congenital myasthenic syndromes are recognised that present early in life. They are caused by inherited mutations affecting a variety of neuromuscular junction proteins, including enzymes involved in ACh synthesis or its breakdown following release, AChRs, and associated proteins that are »

Table 1**Key elements of diagnosis**

Pattern of weakness	History	Clinical examination
Ocular	Diplopia Drooping eyelids	Ophthalmoplegia (check full eye movements) Ptosis (can be unilateral) Look for fatiguability on sustained upgaze Look at old photographs
Bulbar	Inability to smile Difficulty chewing Drooling/nasal regurgitation/ choking episodes	Examine forced eyelid and mouth closure Listen for dysarthria/nasal speech after prolonged speech e.g. at end of consultation/counting to 50
Axial	Head drop Neck pain	Check strength of neck flexion and extension
Limb	Difficulty lifting objects/going up stairs	Examine proximal power before and after repetitive movements, e.g. unilateral shoulder abduction 20 times
Respiratory	Exertional dyspnoea Orthopnoea	Measure forced vital capacity

necessary for the clustering of AChRs.

The thymus has an important role in the pathogenesis of MG. Approximately 15% of cases are associated with a thymoma. In non-thymomatous MG, especially in young patients, the gland is frequently enlarged with lymphocytic infiltrates. The thymus is more frequently atrophic in patients with late-onset MG, and its pathogenic role in this situation is less clear.

PRESENTATION AND CLINICAL COURSE

MG presents with fatiguable painless muscle weakness. Diplopia and ptosis are the most common initial presenting features. Approximately

80% of patients presenting with ocular MG will subsequently develop more generalised weakness. However, if the symptoms remain purely ocular for more than two years, the chance of progression falls to 10%.⁷ Bulbar and facial weakness cause difficulties with speech, chewing and swallowing, and increase the risk of aspiration. Neck weakness can lead to head drop and neck pain. Limb weakness is often proximal. Respiratory muscle weakness, the most serious manifestation of MG, can be fatal.

The mortality rate in MG has dropped markedly from >30% in the 1940s to <5%.⁸ MuSK MG has a relatively greater predilection for

'Respiratory muscle weakness, the most serious manifestation of myasthenia gravis, can be fatal'

bulbar and facial muscles, with a marked female preponderance and a younger age at disease onset. MuSK MG is typically more refractory to treatment and more aggressive immunotherapy may be required.^{1,2}

Table 2**Diagnostic tests**

Test	Comment
ICE test	Crushed ice in a latex glove is placed over closed eyelids for 2 min Positive if ptosis improves by 2 mm Easy to perform but only useful if patient has significant ptosis Sensitivity 90-95%. Specificity near 100% ⁹
Edrophonium	IV acetylcholinesterase inhibitor injected and patient examined for demonstrable improvement in symptoms (e.g. ptosis) Risk of bradyarrhythmias calls for availability of immediate atropine and full resuscitation facilities. Now rarely performed Sensitivity 60-95% ¹⁰
Clinical neurophysiology	Routine nerve conduction studies and electromyogram (EMG) are typically normal Repetitive nerve stimulation elicits a decrementing compound muscle action potential. Sensitivity above 50%, but lower in ocular MG Single fibre EMG looks for an increase in temporal variability of action potentials arising from individual muscle fibres. Sensitivity 82-90% ¹⁰
Immunology	85% of patients with MG are positive for AChR antibodies 40-70% of remainder are positive for MuSK antibodies Both serological tests are highly specific
Mediastinal imaging	When a diagnosis of MG is made, the patient should have CT/MRI of thorax to look for thymic enlargement or a tumour

Patients who are negative for both AChR and MuSK antibodies tend to resemble AChR antibody positive patients in clinical presentation and thymic pathology.⁵

‘The history should elicit the pattern of weakness, severity and diurnal variation’

DIAGNOSIS

A detailed history is the most valuable tool in the diagnosis of MG (see table 1, opposite). The history should elicit the pattern of weakness, severity and diurnal variation. Exacerbating factors including extremes of weather, emotional stress, menstruation and intercurrent illness should be enquired about. Patients with autoimmune MG are more likely to have additional organ-specific autoimmune diseases.

If a diagnosis of MG is suspected on clinical grounds, the patient should be referred to a neurologist as certain serological tests (e.g. MUSK antibodies) and specific electrophysiological tests for MG are only carried out in specialist centres. Immunosuppressive therapy should only be initiated in a specialist setting.

There are a number of diagnostic tests (see table 2, opposite). No one test is 100% sensitive and patients who have negative antibodies and normal neurophysiology may still have MG.

Antibody tests may be repeated as a seroconversion rate of up to 15% has been reported. Some patients may only have antibodies detected on a very specific cell-based assay. In a small number of patients, the diagnosis may be based on meticulous history taking and clinical examination.

TREATMENT

MG treatment should be directed at ameliorating weakness with acetylcholinesterase blockers and modulating the immune system.¹¹ There are, however, relatively few randomised controlled trials.

Acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors reduce the breakdown of ACh following its release into the cleft of the

neuromuscular junction. The European Federation of Neurological Societies recommends their use as first-line treatment for all forms of MG (class IV evidence), although most patients will eventually require immunomodulatory treatment.¹¹ Pyridostigmine is the most widely used, but its short half life means that 3-4 hourly dosing is required, with the dose titrated according to symptoms. Side effects include hypersalivation, lacrimation and diarrhoea. Cholinergic crisis can occur when high doses are used. Anticholinesterases are less effective in MuSK antibody-positive MG.

Immunomodulatory therapy

Most patients with generalised MG require immunomodulatory therapy. Prednisolone is generally used as the first-line agent, although long-term side effects limit its use. The minimum effective dose should be used with appropriate monitoring of bone density and use of bisphosphonates and other bone protection agents. Steroids are anecdotally reported to lead to a transient worsening of myasthenic symptoms, and so prednisolone should be initiated cautiously at a low dose. Patients may require hospital admission for monitoring if the degree of weakness does not allow a very slow escalation of treatment.

Azathioprine is the most widely used second-line immunosuppressive agent. Trial evidence supports its use mainly as a steroid-sparing agent, although it can take 6-24 months to exert this effect.¹² Side effects include leucopaenia and liver toxicity. A thiopurine methyltransferase (TPMT) assay should be requested before commencing treatment as patients with reduced activity of this enzyme become toxic at lower doses. A shared care protocol allows appropriate monitoring of haematological and hepatic parameters.

The place of mycophenolate mofetil in MG is controversial. Two randomised controlled trials failed to demonstrate a significant benefit, but its relatively mild side effect profile continues to attract support for its use.¹³

Methotrexate is preferred by some neurologists, although it is contraindicated in women of child-bearing age.

Third-line immunosuppressive agents used in MG include cyclophosphamide, tacrolimus, ciclosporin and rituximab, although there is a paucity of randomised controlled trial evidence.

Thymectomy

Thymectomy is commonly performed for MG, although again the evidence supporting its use is mainly retrospective. It is indicated when a thymoma is suspected, and most neurologists would advocate its use in patients presenting with MG before the age of 50. There is no evidence that patients with MuSK MG benefit from thymectomy.

MYASTHENIC CRISIS

In spite of the availability of symptomatic and immunomodulatory treatment, up to 20% of patients will experience a myasthenic crisis requiring hospital admission for ventilatory support at some stage of the disease.¹⁴

In this situation intravenous immunoglobulin (IVIG) and plasma exchange are both rapidly effective and can bring about an improvement within a few days, which may avoid the need for endotracheal intubation.

‘Up to 20% of patients will experience a myasthenic crisis requiring admission for ventilatory support’

Their efficacy is similar but IVIG is better tolerated. A small minority of patients with refractory MG require regular admission for IVIG or plasma exchange.

Although MG is eminently treatable its often unpredictable fluctuations and the fear of developing a crisis can make life difficult for patients. Support from specialist nurses and other patients is available from the Myasthenia Gravis Association, see Useful information box, p18. »

key points

SELECTED BY

Dr Peter Saul

GP, Wrexham and associate GP Dean for North Wales

Myasthenia gravis is caused by failure of chemical transmission at the neuromuscular junction. It is an autoimmune disorder in which antibodies interfere with neuromuscular transmission. It has a prevalence of around 20 per 100,000. The incidence is bimodal with a 2:1 female to male ratio in the younger population and a reversed sex ratio over the age of 60. Approximately 15% of cases of myasthenia gravis are associated with a thymoma.

Myasthenia gravis presents with fatiguable painless muscle weakness. Diplopia and ptosis are the most common initial presenting features. Approximately 80% of patients presenting with ocular myasthenia gravis will subsequently develop more generalised weakness. Respiratory muscle weakness is the most serious manifestation of myasthenia gravis and can be fatal.

A detailed history is the most valuable tool in the diagnosis of myasthenia gravis. This should elicit the pattern of weakness, severity and diurnal variation. Exacerbating factors including extremes of weather, emotional stress, menstruation and intercurrent illness should be enquired about. No one diagnostic test is 100% sensitive and patients who have negative antibodies and normal neurophysiology may still have myasthenia gravis.

Treatment should be directed at ameliorating weakness with acetylcholinesterase blockers and modulating the immune system. Pyridostigmine is the most widely used acetylcholinesterase inhibitor, but its short half life means that 3-4 hourly dosing is required, with the dose titrated according to symptoms. Side effects include hypersalivation, lacrimation and diarrhoea. Most patients with generalised myasthenia gravis require immunomodulatory therapy and prednisolone is generally used as the first-line agent.

In spite of the availability of symptomatic and immunomodulatory treatment, up to 20% of patients will experience a myasthenic crisis requiring hospital admission for ventilatory support at some stage of the disease. Although myasthenia gravis is eminently treatable its often unpredictable fluctuations and the fear of developing a crisis can make life difficult for patients.

The GP can provide enormous support to the patient on immunosuppressants. Full blood count as well as liver and renal function must be checked on a regular basis. Steroid-related side effects must also be monitored frequently to ensure that the patient is on appropriate bone protection therapy. The GP may be the first port of call in the case of a sudden worsening of symptoms and in such cases, should refer the patient urgently to their neurology centre for specialist treatment.

CONCLUSION

MG is a chronic disease and the immunosuppressive treatment that is often needed requires a long-term commitment from both the health practitioner and the patient. The GP can provide enormous support to the patient on immunosuppressants. Full blood count as well as liver and renal function must be checked on a regular basis. Steroid-related side effects must also be monitored frequently to ensure that the patient is on appropriate bone protection therapy.

The GP may be the first port of call in the case of a sudden worsening of symptoms and in such cases, should refer the patient urgently to their neurology centre for specialist treatment.

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Useful information

The Myasthenia Gravis Association provides support and advice for patients and their families
www.mga-charity.org

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