Myasthenia Gravis

Myasthenia gravis (MG) is a disorder of neuromuscular transmission, resulting from binding of autoantibodies to components of the neuromuscular junction, most commonly the acetylcholine receptor\[1\]. This leads to muscular weakness with easy ‘fatiguability’, which is worse on exercise and improves with rest.

MG should be classified according to\[2\]:

- The antibody specificity: acetylcholine; muscle-specific receptor tyrosine kinase (MuSK); low-density lipoprotein receptor-related protein 4 (LRP4), or seronegative.
- Thymus histology: thymitis, thymoma, or atrophy.
- Age at onset: child, or aged less than or more than 50 years.
- Type of course: ocular or generalised.

Seronegative MG

- A subgroup of MG patients exists, who are seronegative to the usual tests but have MuSK autoantibodies (in up to 40%)\[3\].
- They are predominantly female, tend to be aged under 40 years, a third failing to respond to anticholinesterase drugs, but nearly half responding to immunosuppression with steroids.

Epidemiology

- The incidence ranges from 0.3 to 2.8 per 100,000. It is estimated to affect more than 700,000 people worldwide\[1\].
- The prevalence of MG in the UK is estimated at about 15 per 100,000 population\[4\].
- Peak incidence is in the third decade for women and the sixth or seventh decade in men\[5\].
- The diagnosis is being made more often in the elderly in whom the sex ratio is roughly equal.

Aetiology

- In most patients, IgG1-dominant antibodies to acetylcholine receptors cause fatigable weakness of skeletal muscles. In the rest, a variable proportion possesses antibodies to MuSK\[6\].
- About 15% of patients with MG have a thymoma and 30-50% of patients with thymoma also have MG\[7\].
- The condition can sometimes be inherited, although there is a predisposition for autoimmune diseases to run in families.
- Online Mendelian Inheritance in Man (OMIM) lists many entries under MG, although most are myasthenic syndromes. Just one is called myasthenia gravis. This suggests an association of MG with HLAB8 and DR3. In terms of underlying genetic abnormalities, work is ongoing\[8\].

Presentation

Almost all MG patients will have ocular manifestations at some point during the course of their disease. Although ocular symptoms are often the first to appear, most patients progress to generalised MG and only 15% continue to have isolated ocular complaints for the entire course of the disease\[9\].

The clinical presentation varies from mild weakness of limited muscle groups (class I, or ocular, MG) to severe weakness of multiple muscle groups (class V, or severe generalised, MG).
Muscle fatigues more readily after exercise:
- This is a feature used in making the diagnosis.
- For example, getting the patient to count up to 50. As the patient nears 50 their voice becomes less audible as they are fatiguing.
- Alternatively, ask the patient to keep their head still and look at your finger, which is held above the forehead level. Thus, the patient has to look up and stay looking up. Patients with ocular muscle involvement are usually unable to do this for more than a few seconds.

- Droop of the upper eyelids is typical with weakness of external ocular muscles producing diplopia. Patients may tilt their head upwards to compensate.
- Weakness is more marked in proximal muscles and isolated weakness of limb muscles is the presenting feature in a minority of patients.
- Weakness of the following muscles may also be seen:
  - Small muscles of the hands (finger extensors).
  - Deltoid and triceps muscles.
  - Bulbar muscles - common, causing a nasal sound to speech that is slurred.
  - Facial muscles - very common, producing an abnormal horizontal smile with a furrowed brow that compensates for ptosis.
  - Muscles involved in chewing - thus eating can become difficult and weak muscles may make the jaw drop so that the patient may sit with chin on hand to support it.
  - Flexors and extensors of the head - are often weak.

- Symmetrical weakness of a number of other muscles may produce difficulty with walking, sitting or even holding the head up.
- There is no muscle wasting or fasciculation. Tone is normal. Sensation is unimpaired and tendon reflexes are normal.
- Seizures may occur.
- People with MG are resistant to suxamethonium (used to provide short-duration neuromuscular blockade for surgery) but can develop dual block resulting in delayed recovery[10].

**Progression**
In the majority of patients, disease progression will take place within the first year after onset and within two years in up to 80% of cases. If patients have restricted ocular disease for two years without developing generalised MG, they are not likely to develop it later. When weakness is limited to the extrinsic ocular muscles and levator palpebrae superioris, the disease is called ocular myasthenia[9].

- The most typical pattern is for disease to spread from mild to moderate or severe over the course of weeks or months, although sometimes the disease can remain restricted to the external ocular muscles and eyelids for years.
- In severe and general weakness it is rare for the ocular muscles to be unaffected.
- Disease is confined to the ocular muscles in only around 15% of patients.
- Intercurrent illness, medications, pregnancy, emotions and hypokalaemia can all exacerbate weakness and may swiftly precipitate a myasthenic crisis and respiratory inadequacy.
- Spontaneous remissions are rare. Full and prolonged remissions are even rarer. Most remissions from treatment occur in the first three years of the disease.

**Respiratory compromise**
Weakness of the muscles of ventilation can cause acute respiratory failure. This is an acute neurological emergency that requires ventilation. Weak pharyngeal muscles can also lead to compromise of the airway.

- Monitoring arterial pO₂ or oxygen saturation is not enough, as vital capacity can decrease markedly before these parameters change.
- The best method is regularly to monitor vital capacity, tidal volume, negative inspiratory force and blood gases in such patients.
Myasthenic crisis

Myasthenic crisis (MC) is a complication of MG characterised by worsening muscle weakness resulting in respiratory failure that requires intubation and mechanical ventilation. MC is a very important, serious and reversible neurological emergency that affects 20-30% of myasthenic patients, usually within the first year of illness; it may be the first indication of the disease.

Most patients have a predisposing factor that triggers the crisis, often a respiratory tract infection. It may present as a postsurgical patient, in whom exacerbation of muscle weakness from MG causes a delay in extubation.

Immunoglobulins, plasma exchange and steroids are the cornerstones of immunotherapy. With modern intensive care, the mortality rate of MC is now less than 5%.

It can be extremely difficult to distinguish between worsening of myasthenia (MC) or excessive anticholinergic medication (cholinergic crisis) when a patient with known MG presents with rapidly increasing muscular weakness, with or without respiratory difficulty.

Features suggestive of a cholinergic crisis (too much medication) include muscle fasciculation, pallor, sweating, hypersalivation and small pupils. If in doubt, perform an edrophonium test. Improvement suggests too little medication, ie MC; however, aggravation suggests too much medication. Be prepared to stop all medication, ventilate and possibly arrange a plasmapheresis. This test should only be performed with the necessary skills and equipment ready for intubation and ventilation.

Potentially dangerous drugs

There are a number of drugs that can aggravate the condition. They should be used with caution if essential but are best avoided:

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Antibiotics</td>
<td>Aminoglycosides - eg, gentamicin</td>
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<tr>
<td></td>
<td>Ciprofloxacin</td>
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<td></td>
<td>Macrolides - eg, erythromycin, azithromycin</td>
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<td></td>
<td>Tetracycline</td>
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<td></td>
<td>Ampicillin</td>
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<td></td>
<td>Clindamycin</td>
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<td>Beta-blockers</td>
<td>Propranolol</td>
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<td></td>
<td>Atenolol</td>
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<tr>
<td></td>
<td>Timolol eyedrops</td>
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<tr>
<td>Anti-arrhythmic drugs</td>
<td>Verapamil</td>
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<tr>
<td></td>
<td>Quinidine and procainamide (both withdrawn)</td>
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<tr>
<td>Neuromuscular blocking agents</td>
<td>Atracurium</td>
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<tr>
<td></td>
<td>Vecuronium</td>
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<tr>
<td></td>
<td>(May cause unexpectedly long paralysis)</td>
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<tr>
<td>Other drugs</td>
<td>Lithium</td>
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<td></td>
<td>D-penicillamine</td>
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<td></td>
<td>Opiates - eg, pethidine</td>
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<td></td>
<td>Phenytoin</td>
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<td></td>
<td>Statins [12]</td>
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<tr>
<td></td>
<td>Magnesium</td>
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<td></td>
<td>Chloroquine</td>
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<td>Prednisolone</td>
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Differential diagnosis

Causes of generalised muscle weakness

- Myasthenic syndromes: diseases of neuromuscular junction result from immune, toxic, genetic pathologies, including:\n  - Lambert-Eaton myasthenic syndrome - associated with small-cell lung cancer; may occur many years before detectable lesion.
  - Autoimmune disorders.
  - Congenital myasthenic syndromes.

- Multiple sclerosis (MS) - hyperreflexia and extensor plantar response can be seen, which help differentiate it from MG.
- Motor neurone disease (MND) - usually features of lower motor neurone (LMN) disease with wasting and fasciculation are present.
- Hyperthyroidism.
- Myalgic encephalomyelitis (ME) - ‘chronic fatigue syndrome’ - will have vague feelings of exhaustion made worse by any effort and no neurological signs to accompany it unless from disuse. The specific tests for MG will be negative.
- Other myopathies - may show fasciculation and elevated creatine kinase (CK).
- Toxins and drugs - eg, botulinum, organophosphate poisoning.
- Acute Guillain-Barré syndrome - the motor type will have LMN features.

Causes of ocular symptoms

- Horner's syndrome - is usually unilateral. The eyelid may droop but the pupil is smaller than the other and sweating is reduced or absent on that side of the face.
- Oculopharyngeal muscular dystrophy.

Bulbar symptoms

- Amyotrophic lateral sclerosis/MND.

Investigations

The diagnosis is based on clinical features, the benefit of cholinesterase inhibitors, the detection of specific autoantibodies (anti-AChR, anti-MuSK or anti-LRP4), and electrophysiological tests.

If the diagnosis of MG is suspected, refer the patient to a neurology unit for further investigations. In patients with ptosis, the ice test is a simple first-line test while waiting for other investigations. This distinguishes MG from other causes of ptosis. Crushed ice in a latex glove is applied to the eye for three minutes. In MG this leads to improvement of ptosis and it has a sensitivity and specificity of over 90%.

Diagnostic tests

- Serum anti-acetylcholine receptor (ACh-R) antibody testing is the first-line investigation for non-urgent patients.
- Thyroid function for all patients.
- Serum MuSK antibody testing for all patients negative for ACh-R antibodies.
- Neurophysiological testing on symptomatic muscles may help to establish the diagnosis in seronegative patients with suspected MG. Repetitive nerve stimulation is the initial test. If this is negative then single-fibre electromyography should be considered.
- MR scan of brain: patients with negative serology and neurophysiology, and with symptoms compatible with ocular myasthenia, may have structural brain disease.
- Thymus CT or MRI scanning for all patients with suspected myasthenia, irrespective of distribution (ocular/generalised) or serology (seropositive/negative).
- Edrophonium (Tensilon®) test if there is diagnostic doubt:
  - The edrophonium (Tensilon®) test involves intravenous administration of a short-acting acetylcholinesterase inhibitor while watching for a transient improvement in muscle strength. Although it has a high sensitivity (95%) for generalised MG, it is now rarely done, as it can result in life-threatening bradycardia and requires immediate access to resuscitation facilities.
Associated diseases\[^{16}\]\n
There is an association between MG and other autoimmune diseases in 25%. They include thyroid disease, dermatomyositis, polymyositis, systemic lupus erythematosus, Addison’s disease, Guillain-Barré syndrome and juvenile rheumatoid arthritis.

Management\[^{2, 17, 18}\]\n
Symptomatic treatment with acetylcholinesterase inhibition is usually combined with immunosuppression. Pyridostigmine is the preferred symptomatic treatment. For patients who do not adequately respond to symptomatic therapy, corticosteroids, azathioprine and thymectomy are first-line immunosuppressive treatments.

Alternative immunosuppressive options to azathioprine include ciclosporin, cyclophosphamide, methotrexate, mycophenolate mofetil and tacrolimus. Rituximab is a promising new drug for severe generalised MG. Emerging therapy options include belimumab, eculizumab and the granulocyte-macrophage colony-stimulating factor.

A Cochrane review found a benefit of intravenous immunoglobulin in the treatment of exacerbations of MG but insufficient evidence to determine whether intravenous immunoglobulin is effective for chronic MG\[^{19}\].

If there is difficulty with swallowing, the diet may need to be modified to aid nutrition and to prevent inhalation.

Newborn babies born to myasthenic mothers are at risk of transient myasthenic weakness (even if the mother's myasthenia is well controlled) and should have rapid access to neonatal high-dependency support\[^{20}\].

Thymectomy

- Thymectomy is important if a thymoma is present but may be beneficial even without one.
- Data from several observational studies suggest that thymectomy could be beneficial for non-thymomatous MG\[^{21}\]. One randomised trial found that thymectomy improved clinical outcomes over a three-year period in patients with non-thymomatous MG\[^{22}\].
- Factors associated with a good response are age less than 60 years, symptoms less than two years and a low dose of pyridostigmine required.

Complications

- \textbf{Aspiration pneumonia} due to throat muscle weakness.
- \textbf{Acute respiratory failure} during an exacerbation.
- Many patients with MG continue to have severe restrictions on their activities of daily living.

Prognosis

Treatments have improved over a period of 30 years, leading to significantly fewer deaths and better quality of life\[^{23}\].

The increasing use of immunomodulating therapies in recent years has been a major factor in improving the prognosis for patients with MG\[^{1}\].

However, while the disease usually responds to standard and nonspecific immunosuppression, current treatments frequently fail to control myasthenic weakness completely or are associated with significant morbidity because of the requirement for long-term immunosuppression\[^{24}\].

Further reading & references


8. Mysaesthenia Gravis, MG; Online Mendelian Inheritance in Man (OMIM)

9. EFNS/ENS Guidelines for the treatment of ocular myasthenia; European Federation of Neurological Societies (2014)

10. British National Formulary; NICE Evidence Services (UK access only)


18. Guidelines for the treatment of autoimmune neuromuscular transmission disorders; European Federation of Neurological Societies (2010)


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