Myasthenia Gravis

Myasthenia gravis (MG) was first described by Thomas Willis in 1672. It is an acquired autoimmune disease with antibodies against the nicotinic acetylcholine receptor (AChR) at the neuromuscular junction or muscle-specific tyrosine kinase (MuSK). This leads to muscular weakness with easy ‘fatiguability’, which is worse on exercise and improves with rest.

Epidemiology

- The prevalence of MG in the UK is estimated at about 15 per 100,000 population.[2]
- Peak incidence is in the third decade for women and the sixth or seventh decade in men.[3]
- The diagnosis is being made more often in the elderly in whom the sex ratio is roughly equal.

Aetiology

- About 10% of patients with MG have a thymoma and around half of patients with thymoma also have MG.
- 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 HLA B8 and DR3. In terms of underlying genetic abnormalities, work is ongoing.[4]
- It can be aggravated by or induced by drug treatment, of which penicillamine is the best documented.
- Most cases are, however, idiopathic.

Presentation

Many patients present with problems of the ocular muscles and most experience them at some stage. 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).[5]

- Muscle fatigues more readily after exercise - 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.[6]
Seizures may occur and there is a case report of undiagnosed MG mistakenly thought to be eclampsia.\[7]\]

There is no muscle wasting or fasciculation. Tone is normal. Sensation is unimpaired and tendon reflexes are normal.

**Progression**

- 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.
- Nearly 90% of patients develop general disease within a year from onset, and onset to maximal weakness is less than 36 years in over 80%.
- 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.
- Choking, drooling and difficulty with chewing or swallowing can produce aspiration pneumonia.

**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 pO\textsubscript{2} 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.
Potentially dangerous drugs

There are a number of drugs that can aggravate the condition and 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><strong>Antibiotics</strong></td>
<td>Aminoglycosides - eg, gentamicin</td>
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<td>Ciprofloxacin</td>
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<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>Clindamycin</td>
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<td><strong>Beta-blockers</strong></td>
<td>Propranolol</td>
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<td></td>
<td>Atenolol</td>
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<td></td>
<td>Timolol eyedrops</td>
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<tr>
<td><strong>Anti-arrhythmic drugs</strong></td>
<td>Verapamil</td>
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<tr>
<td></td>
<td>Quinidine and procainamide (both withdrawn)</td>
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<tr>
<td><strong>Neuromuscular blocking agents</strong></td>
<td>Atracurium</td>
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<tr>
<td></td>
<td>Vecuronium</td>
</tr>
<tr>
<td></td>
<td>(May cause unexpectedly long paralysis)</td>
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<tr>
<td><strong>Other drugs</strong></td>
<td>Lithium</td>
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<td>D-penicillamine</td>
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<td></td>
<td>Opiates - eg, pethidine</td>
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<td></td>
<td>Phenytoin [8]</td>
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<td>Statins [8]</td>
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<td>Magnesium</td>
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<td>Chloroquine</td>
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<td>Prednisolone</td>
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Differential diagnosis

**Causes of generalised muscle weakness**

- **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.
- **Lambert-Eaton myasthenic syndrome** - initially causes slight benefit from exercise before deterioration; no autoantibody or electromyographic (EMG) findings, and ocular weakness does not occur. [9]

**Causes of ocular symptoms**

- **Homer’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

- Ice test:
  - The ice test is a simple first-line test which 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 has a sensitivity and specificity of over 90%.

- Laboratory investigations:
  - The presence of antibodies to the AChR or to MuSK is very specific.
  - About 85% of patients with generalised MG have antibodies to the AChR. 40-70% of the rest are positive for antibodies to MuSK.
  - Repeating negative serological tests can be useful (seroconversion rate of 15% over one year has been reported).
  - Some patients remain seronegative, especially those with only ocular MG.
  - Levels of muscle-specific enzymes such as creatine phosphokinase are usually normal.

- Neurophysiology
  - Routine electrophysiology generally yields normal results in MG.
  - The diagnosis may be missed if specific electrophysiological tests such as repetitive nerve stimulation and single-fibre EMG are not requested.
  - Repetitive nerve stimulation is specific for MG, but the sensitivity is only 70% and is even lower in isolated ocular disease.
  - Single-fibre EMG is a selective recording technique that allows identification of action potentials from individual muscle fibres. It is more sensitive (92-100%) than repetitive nerve stimulation for MG but is not specific. Often only affected muscles will show positive results.

- Edrophonium (Tensilon®) test:
  - 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.

- CT scan of the thorax is required in all patients diagnosed with MG, to exclude the presence of an underlying thymoma.

Associated diseases

There is an association between MG and other autoimmune diseases in 25%. They include thyroid diseases, rheumatoid arthritis, pernicious anaemia and systemic lupus erythematosus (SLE) as well as thymoma or hyperplasia of thymus. In terms of thyroid disorders this may include thyroid eye disease.[1][10]

Management

Reports of vigorously tested trials of management are lacking but it is still regarded as a treatable neurological disorder.

Medical treatment

- Acetylcholinesterase inhibitors provide temporary symptomatic treatment of muscle weakness.[11]
- As the disease becomes more general it is necessary to use immunomodulatory agents like steroids, azathioprine, ciclosporin, and mycophenolate mofetil.
- A Cochrane review found that steroids do appear to be of short-term benefit but there was no difference between steroids, azathioprine and immunoglobulin. However, trials are few.[12]
A more recent study suggests that ciclosporin, either alone or in combination with corticosteroids, may be more beneficial in MG. However, further clinical trials are needed.[13]

There are some data regarding the use of monoclonal antibodies - however, results are disappointing due to the incidence of infections.[14] Rituximab may be beneficial.[15]

Many case series report short-term benefit from plasma exchange in MG, especially in myasthenic crisis. There is insufficient evidence to determine whether plasma exchange improves the long-term outcome for MG.[16]

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.[17]

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

Thymectomy

- Thymectomy is important if a thymoma is present but may be beneficial even without one.
- There are no randomised controlled trials regarding the efficacy of thymectomy on non-thymomatous MG. Data from several observational studies suggest that thymectomy could be beneficial.[18]
- Factors associated with a good response are age less than 60 years, symptoms less than two years and low dose of pyridostigmine required.

Myasthenic versus cholinergic crisis

It can be extremely difficult to distinguish between worsening of myasthenia or excessive anticholinergic medication 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 myasthenic crisis, but 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.

Complications

- Aspiration pneumonia due to throat muscle weakness.
- Acute respiratory failure during an exacerbation.
- Babies born to mothers with the disease may show transient signs due to antibodies crossing the placenta. Antibodies are present in nearly all babies but only 10-20% have symptoms. It may not present until 10-14 days after birth. Babies are also more likely to have arthrogryposis multiplex.

Prognosis

- A typical picture involves exacerbations and remissions.
- Without treatment there is a mortality of 25-30% but, with modern management of crises, there is only a small increased mortality rate.
- Due to improved diagnostic testing, immunotherapy, and intensive care, the prognosis is now favourable with less than 5% mortality and nearly normal life expectancy.[11]
- Intercurrent infection and hot weather can aggravate features.

Seronegative myasthenia gravis

- There is evidence to suggest that a subgroup of MG patients exists, who are seronegative to the usual tests but have MuSK autoantibodies (in up to 40%).[19]
- 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.
- At the end of a period of observation, six (35%) patients were in remission, five (30%) improved, four (24%) were unchanged, and two (12%) had died.
- They concluded that patients with antibodies to MuSK have characteristic clinical features that are different from features of the remaining seronegative MG patients.
Myasthenic syndrome

- Causes include:
  - Lambert-Eaton myasthenic syndrome - associated with small-cell lung cancer; may occur many years before detectable lesion.[20]
  - Autoimmune disorders.

- Underlying aetiology is antibodies directed towards presynaptic calcium channels.
- Tends not to affect the eyes but the proximal muscles of limbs.
- Repeated contraction of muscles can actually increase muscle strength.
- Autonomic dysfunction and hyporeflexia are also seen.
- No, or little, response in the edrophonium (Tensilon®) test.
- Management includes 3,4-diaminopyridine which increases the release of acetylcholine from presynaptic nerve endings.
- There is no role for immunosuppression; however, treatment of the underlying cause can lead to much improvement.

Further reading & references

- Guidelines for the treatment of autoimmune neuromuscular transmission disorders; European Federation of Neurological Societies (2010)
- EFNS/ENS Guidelines for the treatment of ocular myasthenia; European Federation of Neurological Societies (2014)

1. Juel VC, Massey JM; Myasthenia gravis. Orphanet J Rare Dis. 2007 Nov 6;2(1):44.
4. Myaesthenia Gravis, MG; Online Mendelian Inheritance in Man (OMIM)

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