Myasthenia gravis (MG) is the most common primary disorder of neuromuscular transmission. It is characterised clinically by fluctuating painless muscle weakness, which worsens with exercise and towards the end of the day, and improves with rest. It is usually caused by antibodies to postsynaptic proteins, of which three – namely nicotinic acetylcholine receptor (AChR), muscle-specific tyrosine kinase (MuSK) and low-density lipoprotein receptor-related protein 4 (LRP4) – have been identified. Advances in pulmonary and ventilatory support in conjunction with treatments developed based on the understanding of the pathophysiology of the disease have made MG one of the most treatable neurological disorders.

MG can present to or involve a wide variety of specialists such as internal medicine physicians, GPs, neurologists, ophthalmologists, otorhinolaryngologists, respiratory physicians, cardiothoracic surgeons, oncologists and intensive care specialists. Since the response of MG to treatment is generally favourable, early recognition and prompt treatment is essential in reducing morbidity and mortality from MG. The aim and scope of this review is to provide an up-to-date, practical and relevant overview of this eminently treatable condition.

Epidemiology

The annual incidence of MG is reported to range between 3 and 30 per million population, with the rates at the upper end of the range reported by prospective studies probably providing the most accurate estimates.1 The incidence rates have increased over time due to greater disease awareness and better diagnostic methods. The prevalence of MG is reported to be approximately 200 per million population now,2 compared with about 5 per million population between 1915 and 1934.3 This increase can be explained by an aging population, better detection of the antibodies to postsynaptic proteins and longer survival from treatment advances.4 The influence of geography on incidence and prevalence is difficult to ascertain as most studies have been carried out in Europe and North America.1,5

In both females and males, the incidence of MG increases with age. Some studies report a bimodal dis-
Review Myasthenia gravis

Clinical presentation
The extraocular muscles are initially affected in 50-60 per cent of cases, but virtually all patients will have ocular involvement within two years of disease onset. MG remains purely ocular in 15 per cent of cases. Only 15 per cent of patients progress from ocular MG to generalised MG after two years of disease duration. When MG generalises, the symptoms of muscle weakness typically progress in a craniocaudal direction: from the ocular muscles, to the facial muscles, to the lower bulbar muscles, to the truncal muscles, and finally to the limb muscles. Symptom onset to maximal weakness occurs within the first two years in more than 80 per cent of cases. Despite modern treatments, at least 20 per cent of patients will experience a myasthenic crisis, defined as weakness necessitating intubation and mechanical ventilation, usually within the first two years of diagnosis.

Ptosis, due to levator palpebrae weakness, may be unilateral. Extraocular muscle weakness may mimic third, fourth or sixth cranial nerve palsies, or internuclear ophthalmoplegia. Difficulty with eye closure suggests weakness of the orbicularis oculi. Facial muscle weakness may result in an expressionless face, or a ‘snarl’ when the patient tries to smile. Jaw weakness may interfere with mastication. Nasal speech and nasal regurgitation may occur with palatal weakness, while dysphagia, dysarthria and choking may result from weakness of the pharyngeal and tongue musculature. Dyspnoea can occur with laryngeal weakness. In mild disease, neck flexion weakness may be the only finding. Neck extension weakness causes a ‘head drop’. Upper extremity weakness is commoner than lower extremity weakness. Mental and physical fatigue are very common features, and can be debilitating.

Physical examination should aim to demonstrate pathological fatigability of muscle strength. Manoeuvres that may be used include asking the patient to look up for several minutes (examining for ptosis or extraocular muscle weakness), counting aloud to 100 (listening for a nasal or slurred speech), and repetitively testing the strength of proximal muscles (looking for increasing muscle weakness). If a patient has generalised muscle weakness with no ocular involvement, the diagnosis of MG should be questioned.

Muscle weakness in MG can be exacerbated by emotional upset, hot temperature, infection, men-

Table 1. Drugs that may exacerbate myasthenia gravis

<table>
<thead>
<tr>
<th>Type of agent</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-infective agents</td>
<td>Aminoglycosides, antimalarials, macrolides, polymyxins</td>
</tr>
<tr>
<td>Antiirheumatics</td>
<td>D-penicillamine, hydroxychloroquine</td>
</tr>
<tr>
<td>Cardiovascular agents</td>
<td>Beta-blockers, calcium-channel blockers</td>
</tr>
<tr>
<td>Neuromuscular blockers</td>
<td>Non-depolarising drugs, depolarising drugs</td>
</tr>
<tr>
<td>Topical eye preparations</td>
<td>Drugs that contain polymyxins, beta-blockers</td>
</tr>
</tbody>
</table>

Aetiopathogenesis
Autoantibodies
MG is caused by antibodies against proteins in the neuromuscular junction postsynaptic membrane (see Figure 1). Antibodies against AChR are detectable in 50 per cent of MG cases and 85 per cent of generalised MG cases. The anti-AChR antibodies are pathogenic because they reduce the number of AChRs at the neuromuscular junction via three mechanisms:
- anti-AChR antibodies bind and crosslink the AChRs, resulting in increased endocytosis and degradation of AChRs by the muscle cell;
- anti-AChRs bind complement factors at the postsynaptic membrane, leading to focal lysis of the postsynaptic folds at the neuromuscular junction by the membrane attack complex; and
- the destruction of other AChR-associated proteins, such as utrophin, rapsyn and voltage-gated sodium channels, impairs neuromuscular transmission as these proteins are involved in neuromuscular junction formation and maintenance.

In up to 70 per cent of patients with no detectable anti-AChR antibodies, antibodies against MuSK, a transmembrane protein located at the postsynaptic membrane of the neuromuscular junction, which is functionally interactive with AChR, have been detected. The pathogenic mechanisms of anti-MuSK antibodies are incompletely understood, but appear to involve disrupting the membrane ultra-
structure and electrophysiological function of MuSK, and the disassembly of AChR clusters. The prevalence of anti-MuSK antibody-positive MG is higher in countries nearer the equator. Anti-MuSK antibodies appear to produce a distinct clinical phenotype, with patients more commonly female, a predominance of cranial and bulbar muscle involvement with a higher frequency of respiratory crises, less limb involvement and being uncommonly associated with long-term pure ocular MG.

Approximately 15 per cent of all patients with generalised MG have no detectable serum anti-AChR or anti-MuSK antibodies. These patients are considered to have seronegative MG. In up to two-thirds of seronegative MG patients, low-affinity anti-AChR antibodies have been demonstrated on a special cell-based assay where the AChRs are clustered together with the protein rapsyn.

Recently, a new antigen target at the neuromuscular junction, known as low-density lipoprotein receptor-related protein 4 (LRP4), has been identified. LRP4 is an agrin receptor and is required for agrin-induced activation of MuSK, AChR clustering and neuromuscular junction formation. The pathogenic role of anti-LRP4 antibodies appears to involve inhibiting interactions between agrin and LRP4, and reducing AChR clustering. The frequency of anti-LRP4 antibodies in patients with MG appears to vary depending on geographical location, ranging from 2 per cent in Japan to 50 per cent in Germany. A proportion of patients have both anti-LRP4 and anti-MuSK antibodies. It has been reported that the major clinical features of anti-LRP4 antibody-positive MG are not very different from those of anti-AChR antibody-positive MG. About 5 per cent of generalised MG patients who continue to have undetectable antibodies probably have pathogenic antibodies against as yet undefined muscle membrane proteins that interact with AChRs.

Up to 30 per cent of anti-AChR antibody-positive MG patients have additional antibodies that bind to epitopes on skeletal and heart muscle tissue, known as anti-striational antibodies. Anti-striational antibodies to the sarcomeric protein titin, the sarcoplasmic calcium channel ryanodine receptor and the α-subunit of the muscular voltage-gated potassium channel (Kv1.4) have been extensively investigated. Anti-striational antibodies do not have a major pathogenic role, but are markers for thymoma and late-onset disease. They are also associated with autoimmune myocarditis and myositis, and lethal arrhythmias. Although MG patients with anti-Kv1.4 antibodies have been associated with severe disease in a Japanese population, a recent study in a Caucasian population demonstrated that the presence of these antibodies was associated with mild MG, suggesting different clinical phenotypes between the two populations.

**Thymus**

The thymus is thought to play an important pathogenic role in anti-AChR antibody-positive MG, with thymic hyperplasia present in 65 per cent of cases and thymoma present in 10 per cent of cases. Furthermore, MG occurs in 30 per cent of patients with a thymoma as a paraneoplastic phenomenon. A large body of evidence implicates the thymus as the main site of autosensitisation. AChR expression by myoid cells in the thymus, in the presence of the inflammatory environment within the thymus, is thought to lead to the induction and maintenance of the anti-AChR autoimmune response in MG. In anti-MuSK antibody-positive patients, there are minimal thymic changes, suggesting no pathogenic role of the thymus in this subtype. In anti-LRP4 antibody-positive MG patients, no thymus disorder has been established thus far.

**Genetic and environmental factors**

Certain human leukocyte antigen (HLA) loci and several common variants in HLA-unlinked genes have been associated with MG susceptibility. Many of these risk-associated genes are widely distributed among other autoimmune diseases, suggesting shared pathogenic pathways. Indeed, first-degree relatives of MG patients have a higher incidence of other autoimmune diseases.

Several pathogens, such as the Epstein-Barr virus and poliovirus, have been suggested as potential candidates for driving and perpetuating autoimmunity in MG. However, many of the studies give contradictory and inconsistent results.

**Diagnostic investigations**

The differential diagnosis of MG is wide (see Table 2). A detailed history and physical examination in conjunction with investigations is often needed to provide diagnostic clues. A systematic review examining the utility of diagnostic tests in MG concluded that only anti-AChR antibody testing and single-fibre electromyography (SFEMG) were adequately validated. However, the anti-MuSK antibody test was not evaluated in this study.

**Antibody tests**

All patients with suspected MG should be tested for anti-AChR antibodies. The sensitivity of this test is 70-
95 per cent for generalised MG and 50-75 per cent for ocular MG. Anti-AChR antibody concentrations do not reliably predict disease severity in individual patients. If anti-AChR antibodies are negative, anti-MuSK antibodies should be tested. In seronegative patients, there is a seroconversion rate of 15 per cent after one year. Immunosuppression can occasionally lead to disappearance of antibodies. Detection of anti-striational antibodies may give an indication of the disease phenotype and prognosis.

Neurophysiology
Repetitive nerve stimulation (RNS) and SFEMG are the most commonly used neurophysiological tests. Results can be misleading in patients on chronic high-dose acetylcholinesterase inhibitors. If there is doubt, then it is better, if possible, to stop these drugs for up to a week before the tests. Detailed descriptions of the methodology behind RNS and SFEMG are beyond the scope of this article, but a brief overview of the main principles of these tests, including their sensitivities and specificities are discussed.

RNS at stimulation rates of 3-10 Hz typically produces a progressive decrement in the amplitude of the compound muscle action potential. The test is approximately 80 per cent positive in generalised MG, but may be negative in 50 per cent of ocular MG. Overall, sensitivity is approximately 75 per cent. The specificity of RNS is variable and depends partly on which nerve is tested.

SFEMG is the most sensitive diagnostic test in MG and should be performed if RNS is normal and a neuromuscular junction disorder is suspected. It shows increased jitter (trial-to-trial variation in the latency from stimulus to response) and intermittent impulse ‘blocking’ (failure of excitation of muscle fibers) in MG. Sensitivity of SFEMG is as high as 99 per cent in generalised MG and is approximately 80 per cent in ocular MG. The specificity of SFEMG is variable and an abnormal test can be seen in other conditions such as mitochondrial cytopathy, motor neurone disease or radiculopathy.

Edrophonium test
The edrophonium or tensilon test is a bedside test in which edrophonium chloride, a short-acting acetylcholinesterase inhibitor, is administered. The aim is to demonstrate reversibility of muscle weakness and can only be performed if there is unequivocal weakness present that can be measured objectively. It should be performed double-blind and placebo-controlled. The sensitivity of the test is as high as 88 per cent for generalised MG and 92 per cent for ocular MG, with specificities of 97 per cent for both disease forms. It is prudent to administer atropine prophylactically because of the risk of bradykinesia and cardiac arrest. It is probably best to avoid doing the test in the elderly.

Ice pack test
A quick method to distinguish ptosis due to MG from other causes is the ice pack test. An ice cube is placed over the drooping eyelid for about two minutes, and if there is improvement in the ptosis, it suggests a neuromuscular transmission disorder. Results pooled from six studies gave this test a sensitivity of 89 per cent and a specificity of 100 per cent.

Imaging
All MG patients should have computed tomography (CT) or magnetic resonance imaging (MRI) of the
Thorax to screen for thymoma or thymic hyperplasia. Imaging of the mediastinum should be repeated in the context of a MG relapse after a period of stable disease to exclude the development of a thymoma, which can occur later in the disease course.

**Treatment**

In MG, treatment strategies tend to vary even among different physicians practising within the same country. There are no UK guidelines and treatment depends on the experience and familiarity of the treating physician to a particular regimen. Figure 2 depicts a general treatment flowchart that I regularly use, but it is important to note that treatment regimens should be individualised as no single treatment strategy is appropriate for every patient. The present day prognosis of MG is excellent with current treatment regimens having reduced the disease mortality from 70 per cent between 1915 and 1934 to less than 5 per cent now. The quality of the scientific evidence for the use of the various treatments in MG is variable (see Table 3).

**Symptomatic treatment**

The first-line symptomatic treatment is acetylcholinesterase inhibitors, usually pyridostigmine. Other acetylcholinesterase inhibitors are rarely used because of their inferior pharmacodynamic profiles and tolerability. Two observational studies concluded that pyridostigmine was more effective than neostigmine with fewer adverse events.

Increasing tolerance to pyridostigmine over time may necessitate dose escalation. Anti-MuSK antibody-positive patients tend to show non-responsiveness to pyridostigmine. High doses of pyridostigmine may lead to desensitisation of AChRs, inducing muscle weakness leading to a cholinergic crisis, which can be difficult to distinguish from a myasthenic crisis. If there is any concern, pyridostigmine can be temporarily withdrawn and the patient monitored for improvement. The majority of MG patients will fail to achieve adequate response on pyridostigmine alone and will require further immunosuppression.

**Short-term immunosuppression**

Oral prednisolone is the most commonly used first-line short-term immunosuppressant. Two double-blind trials of corticosteroids versus placebo gave conflicting results, while one open-label randomised trial comparing high-dose corticosteroid versus low-dose corticosteroid showed no significant difference in efficacy. Prednisolone is typically used...
## Table 3. Treatment options and recommendations in myasthenia gravis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mode of action</th>
<th>Evidence class*</th>
<th>Serious adverse events</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptomatic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>Inhibits acetylcholinesterase</td>
<td>Class III</td>
<td>Cholinergic crisis</td>
<td>First line</td>
</tr>
<tr>
<td><strong>Short-term immunosuppression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Inhibits T-cell activation and impairs function of cells from the monocyte/macrophage lineage</td>
<td>Class II</td>
<td>Cushingoid features, diabetes, hypertension, osteoporosis, psychiatric disorders</td>
<td>First line</td>
</tr>
<tr>
<td><strong>Long-term immunosuppression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Purine antagonist that inhibits DNA synthesis and cell proliferation</td>
<td>Class I</td>
<td>Haematopoietic suppression, hepatotoxicity, malignancy, pancreatitis</td>
<td>First line</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>Calcineurin-mediated inhibition of T-cell interleukin-2 production</td>
<td>Class I</td>
<td>Hypertension, malignancy, nephrotoxicity</td>
<td>To be considered in patients intolerant of or unresponsive to azathioprine, methotrexate, mycophenolate mofetil or tacrolimus</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>DNA-alkylating agent that blocks cell proliferation</td>
<td>Class I</td>
<td>Bladder toxicity, haematopoietic suppression, infertility, malignancy, opportunistic infections</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Folate antagonist that inhibits de novo synthesis of purines and pyrimidines</td>
<td>Class II</td>
<td>Haematopoietic suppression, hepatotoxicity, pneumonitis</td>
<td>Second line in patients intolerant of or unresponsive to azathioprine, methotrexate, mycophenolate mofetil, tacrolimus or ciclosporin</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Inhibits T-cell proliferation by blocking purine synthesis</td>
<td>Class I</td>
<td>Haematopoietic suppression, hepatotoxicity, opportunistic infections</td>
<td>Third line in patients intolerant of or unresponsive to azathioprine, methotrexate or tacrolimus</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Chimeric monoclonal antibody against the B-cell surface marker CD20</td>
<td>Class IV</td>
<td>Neutropaenia, opportunistic infections, progressive multifocal leukoencephalopathy</td>
<td>To be considered only in patients with severe refractory MG unresponsive to other treatments</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Calcineurin-mediated inhibition of T-cell interleukin 2 production</td>
<td>Class I</td>
<td>Hyperglycaemia, hypertension, malignancy, nephrotoxicity</td>
<td>Third line in patients intolerant of or unresponsive to azathioprine, methotrexate or mycophenolate mofetil</td>
</tr>
<tr>
<td><strong>Rapid short-term immunomodulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunoglobulin</td>
<td>Interference of signalling via Fc receptors, neutralisation of activated complement, suppression of idiotypic antibodies, modulation of proinflammatory cytokines</td>
<td>Class I</td>
<td>Aseptic meningitis, solute-induced renal failure, thrombotic complications, volume overload</td>
<td>First line</td>
</tr>
<tr>
<td>Plasma exchange</td>
<td>Removes circulating antibodies, cytokines, immune complexes, and other inflammatory mediators</td>
<td>Class I</td>
<td>Air embolism, disturbances in acid-base homeostasis, hypocalcaemia, hypotension, infection, pneumothorax, thrombosis, volume overload</td>
<td>First line</td>
</tr>
<tr>
<td><strong>Long-term immunomodulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thymectomy</td>
<td>Disrupts B-cells producing anti-AChR antibodies</td>
<td>Class II</td>
<td>General risks of surgery</td>
<td>Always indicated in patients with a thymoma; in non-thymomatous anti-AChR antibody-positive patients, to be considered if MG is not controlled adequately with medical treatment</td>
</tr>
</tbody>
</table>

*Evidence Class I - randomised controlled trials available; Class II - controlled trials without randomisation or randomised trials with small patient number; Class III - uncontrolled trials; Class IV - case series
as an interim measure while titrating up doses of other immunosuppressants and waiting for those to have maximum effect. A ‘steroid dip’ due to a temporary worsening of MG four to ten days after starting prednisolone may occur if prednisolone is started at a high dose. To avoid this, it is recommended that prednisolone be started at a low dose on alternate days and gradually titrated upwards. In certain cases, a daily prednisolone regimen may be more suitable, for example in diabetic patients or those intolerant to the fluctuations inherent to an alternate day regimen. Premature or rapid tapering of corticosteroids should be avoided as this is likely to lead to a relapse of symptoms.

**Long-term immunosuppression**

Several different immunosuppressants are used as long-term corticosteroid-sparing agents in MG. Azathioprine is the most frequently used. A randomised unblinded trial of azathioprine plus initial prednisolone versus prednisolone alone, and another randomised double-blind trial of azathioprine plus prednisolone versus prednisolone plus placebo have established the efficacy of azathioprine in MG. When azathioprine is not tolerated or if the MG remains difficult to control, alternative immunosuppressants can be used including methotrexate (commonly used second line), mycophenolate mofetil or tacrolimus.

A single-blind trial of methotrexate versus azathioprine demonstrated similar efficacy between the two drugs. Two randomised controlled trials failed to show that mycophenolate mofetil plus prednisolone was more effective than prednisolone plus placebo. Several reasons have been suggested for these negative results: the generally mild disease status of patients, the better than expected response to prednisolone and the relatively short duration of the trials. A randomised double-blind placebo-controlled trial of tacrolimus plus prednisolone versus prednisolone plus placebo, and another randomised unblinded non-placebo controlled trial of tacrolimus plus corticosteroids with or without plasma exchange versus no tacrolimus plus corticosteroids with or without plasma exchange have demonstrated that tacrolimus is efficacious in the treatment of MG.

Ciclosporin or cyclophosphamide are reserved for severe cases of MG refractory to the other previously mentioned immunosuppressants, but their use is limited by potentially serious adverse events. A randomised double-blind trial of ciclosporin monotherapy versus placebo, and another randomised double-blind trial of ciclosporin plus prednisolone versus prednisolone plus placebo have clearly shown that ciclosporin is effective in MG. Cyclophosphamide was shown to be effective in a randomised double-blind trial of intravenous pulsed cyclophosphamide plus prednisolone versus prednisolone plus placebo. Rituximab is a useful option in severe refractory MG unresponsive to other treatments, but this treatment is very expensive.

**Rapid short-term immunomodulation**

Intravenous immunoglobulin (IVIG) or plasma exchange (PE) is used in acute severe exacerbations of generalised MG or to optimise muscle strength prior to surgery. IVIG and PE are equal first-line treatments because they have similar efficacy. However, because IVIG is easier to administer and associated with fewer adverse events than PE, the former is often preferred. Two randomised controlled trials comparing IVIG with placebo established the efficacy of this treatment in acute severe MG. Two randomised controlled trials comparing IVIG to PE showed no significant differences between the two treatments in acute exacerbation of MG or in chronic moderate-to-severe MG. One randomised controlled trial of IVIG versus corticosteroids and another of PE versus corticosteroids did not reveal significant differences between the treatments tested.

**Long-term immunomodulation**

Thymectomy is always indicated in patients with a thymoma because of its malignant potential. However, tumour removal does not always lead to remission of MG. Indeed, MG in thymomatous patients is commonly more severe than in non-thymomatous patients.

Thymectomy has been a mainstay of treatment for non-thymomatous MG for over 50 years. However, randomised trials of thymectomy versus medical treatment are lacking. A rigorous evidence-based analysis of 28 studies published between 1953 and 1998 concluded that it only ‘might’ improve the chance of remission as the benefit of surgery was generally small. Thymectomy within the first three years of diagnosis may lead to a better response. The procedure is commonly restricted to patients under the age of 60-65 years because older patients usually have an atrophic thymus. Anti-MuSK antibody-positive patients tend to have a poorer response, probably explained by the lack of typical thymus pathology in these patients. There is controversy as to whether a minority of seronegative MG patients benefit from thymectomy. An ongoing international thymectomy
trial in non-thymomatous patients may help clarify further the right candidates for thymectomy.

Conclusion

Advances in our understanding of the pathophysiology of MG have led to more effective treatments for this condition. Earlier disease recognition combined with prompt appropriate treatment are key factors in improving the prognosis of MG. Therefore, the need to educate and improve disease awareness is important in the diagnosis and management of this eminently treatable neurological disorder.

Declaration of interests

None declared.

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References