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Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity

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Abstract

Acquired myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction in which patients experience fluctuating skeletal muscle weakness that often affects selected muscle groups preferentially. The target of the autoimmune attack in most cases is the skeletal muscle acetylcholine receptor (AChR), but in others, non-AChR components of the neuromuscular junction, such as the muscle-specific receptor tyrosine kinase, are targeted. The pathophysiological result is muscle endplate dysfunction and consequent fatigable muscle weakness. Clinical presentations vary substantially, both for anti-AChR positive and negative MG, and accurate diagnosis and selection of effective treatment depends on recognition of less typical as well as classic disease phenotypes. Accumulating evidence suggests that clinical MG subgroups might respond differently to treatment. In this Review, we provide current information about the epidemiology, immunopathogenesis, clinical presentations, diagnosis, and treatment of MG, including emerging therapeutic strategies.

Introduction

Acquired myasthenia gravis (MG) is a prototypical, antibody-mediated autoimmune disorder of the neuromuscular junction (NMJ).[1] In most cases, it is caused by pathogenic autoantibodies directed towards the skeletal muscle acetylcholine receptor (AChR).[2] In others, non-AChR components of the postsynaptic muscle endplate, such as the muscle-specific receptor tyrosine kinase (MUSK), might serve as targets for the autoimmune attack.[3] The precise origin of the autoimmune response in MG is not known, but abnormalities of the thymus gland (hyperplasia and neoplasia) almost certainly play a part in patients with anti-AChR antibodies, [4,5] and genetic predisposition is also likely to influence which patients develop the disorder.[6] Fluctuating muscular weakness that increases with effort is the characteristic manifestation of MG. A wide range of clinical presentations and associated features allow classification of MG into subtypes based on disease distribution (ocular *vs* generalised), age at onset, thymic abnormalities, and autoantibody profiles. Appropriate recognition of these clinical subtypes helps to determine management strategies and prognosis.

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Conflicts of interest

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In this Review, we address the latest concepts in the immunopathogenesis of MG relevant to the clinical subtypes, including the role of genetic factors that underlie individual susceptibility to the disease. We discuss the importance of clinical recognition of the various presentations of MG, and the available tests that help to confirm the diagnosis. Finally, we review the evidence that supports the various therapeutic modalities in MG, and develop a current, hierarchical approach to its treatment. Emerging treatment strategies are also delineated, including the prospect of antigen-specific therapy.

Epidemiology

MG is a relatively uncommon disease, although prevalence has increased over time with recent estimates approaching 20 per 100 000 in the US population.[7] This increased prevalence is most likely to be due to improved diagnosis and treatment of MG, and an increasing longevity of the population in general. Incidence varies widely from 1.7 to 10.4 per million, depending on the location of study, [8] and has been reported to be as high as 21 per million in Barcelona, Spain.[9] The occurrence of MG is influenced by sex and age: women are affected nearly three times more often than men during early adulthood (aged <40 years), whereas incidence is roughly equal during puberty and after the age of 40 years.[10] After 50 years of age, incidence is higher in men.[10] Childhood MG is uncommon in Europe and North America, comprising 10–15% of MG cases, [7] but is much more common in Asian countries such as China, where up to 50% of patients have disease onset under the age of 15 years, many with purely ocular manifestations.[11]

Clinical presentation

The clinical hallmark of MG is fatigable weakness, usually involving specific susceptible muscle groups. Patients often note that their weakness fluctuates from day to day or even from hour to hour, worsens with activity, and improves with rest. Patients can have varying degrees of ptosis, diplopia, dysarthria, dysphagia, dyspnea, facial weakness, or fatigable limb or axial weakness (panel 1). Ocular weakness, presenting as fluctuating ptosis and/or diplopia, is the most common initial presentation of MG, occurring in approximately 85% of patients.[10] Disease progression to generalised weakness usually occurs within 2 years of disease onset. Weakness of facial muscles is quite common and many patients with MG have detectable weakness of eyelid closure with or without lower facial weakness when examined carefully, even when these muscle groups are not symptomatically weak. Bulbar weakness, presenting with painless dysphagia, dysarthria, or chewing difficulties, is the initial symptom in up to 15% of patients.[12] The relative absence of ocular symptoms in these patients might erroneously suggest a diagnosis of motor neuron disease. Weakness involving respiratory muscles is rarely the presenting feature of the disease, but can be life-threatening, requiring immediate therapeutic action. Although rare, a prominent limb-girdle distribution of weakness or even focal weakness in single muscle groups can occur.[13,14]

Panel 1: **Clinical features of autoimmune myasthenia gravis**

Signs and symptoms

Ocular

- Ptosis—asymmetric, fatigues with upgaze
- Diplopia—the most commonly involved extraocular muscle is the medial rectus

Bulbar

- Dysarthria—lingual, buccal, palatal (nasal speech)

- Dysphagia—excessive clearing of the throat, recurrent pneumonias (subtle signs)
- Dysphonia—hoarseness
- Masticatory weakness—jaw fatigue, jaw closure more affected than jaw opening

Facial

- Eyelid closure—inability to bury eyelashes with forced eye closure
- Lower face—poor cheek puff, drooling

Limb muscles

- Commonly proximal, symmetric
- Arms more affected than legs
- Rarely focal

Axial muscles

- Neck flexion
- Neck extension (head drop)

Respiratory muscles

- Exertional dyspnea—poor inspiratory sniff, cough
- Orthopnea, tachypnea
- Respiratory failure

Distribution of weakness10

- Ocular 17%
- Ocular and bulbar 13%
  - Mild 2%
  - Moderate/severe 11%
- Ocular and limb 20%
- Generalised 50%
  - Mild 2%
  - Moderate 14%
  - Severe 15%
  - Assisted ventilation 11%
  - Died despite ventilation 8%

The course of MG is variable. Many patients experience intermittent worsening of symptoms triggered by infections, emotional stress, surgeries, or medications, particularly during the first year of the disease. Progression to maximum severity typically occurs within the first 2 years of onset.[10] Spontaneous long-lasting remissions are uncommon, but have been reported in 10–20% of patients.[10]

MG subtypes

Differences in clinical presentation, age at onset, autoantibody profile, and the presence or absence of thymic pathology allow identification of several MG clinical subtypes (table 1). Patients with generalised MG can be divided into early-onset and late-onset disease, with early-onset MG usually defined as beginning before the age of 40 years.[15] These patients are more often female, have anti-AChR antibodies, and enlarged, hyperplastic thymus glands. In addition to anti-AChR antibodies, other organ-specific autoantibodies might be present, and patients might be affected by other autoimmune diseases, most commonly autoimmune thyroid disease.[16,17] Antibodies to non-AChR muscle components are not typically seen in early-onset MG.[18]

Patients with onset after the age of 40 years are more often male and usually have normal thymic histology or thymic atrophy. However, there are relatively few histological studies in this age group because thymectomy is rarely done in patients over the age of 50 years unless they have a thymoma. Patients with late-onset MG can present with ocular or generalised weakness, but typically have a more severe disease course compared with early-onset MG, and spontaneous remissions are rare.[19] In addition to anti-AChR antibodies, these patients usually have antibodies to striated muscle proteins such as titin and the ryanodine receptor.[20] The presence of these anti-muscle antibodies, particularly anti-ryanodine receptor antibodies, has been associated with more severe, generalised, or predominantly oropharyngeal weakness, and frequent myasthenic crises.[21,22]

About 10–15% of patients with MG have a thymic epithelial tumour—a thymoma. Thymoma-associated MG is equally common in men and women, and can occur at any age, with peak onset at the age of 50 years.[23,24] Clinical presentations tend to be more severe than in non-thymomatous patients with early-onset MG, commonly with progressive generalised and oropharyngeal weakness. However, long-term prognosis is similar to that of late-onset, non-thymomatous MG.[25–27] With rare exceptions, [28] MG patients with thymoma have high titres of anti-AChR antibodies, and they usually also have antibodies against titin.[23] Additional paraneoplasia-associated antibodies (and their related syndromes) might occur in thymomatous MG, including anti-voltage-gated K^+ and Ca^{2+} channel, anti-Hu (antineuronal nuclear autoantibody 1), anti-dihydropyrimidinase-related protein 5 (formerly anti-collapsin response mediator protein 5), and anti-glutamic acid decarboxylase antibodies.[29] The presence of autoantibodies to a voltage-gated K^+ channel, KCNA4 (formerly $K_V1.4$), has been recently reported in Japanese patients with severe MG, thymoma, and concomitant myocarditis and/or myositis.[30] In patients with thymoma, surgery (thymothymectomy) often completely and permanently removes the tumour, but symptoms of MG usually persist and require chronic immunotherapy.

Approximately 15% of patients with generalised MG do not have anti-AChR antibodies on current assay methods. In about 40% of these patients, antibodies to MUSK, another postsynaptic NMJ protein, are found.[31] Whereas patients with anti-MUSK antibodies can have presentations similar to anti-AChR-positive MG, they commonly have atypical clinical features, such as selective facial, bulbar, neck, and respiratory muscle weakness and marked muscle atrophy, occasionally with relative sparing of ocular muscles.[32,33] Respiratory crises are more common than in generalised anti-AChR-positive disease. Weakness can involve muscles that are not usually symptomatic in MG, such as paraspinal and upper oesophageal muscles.[34] Enhanced sensitivity, non-responsiveness, or even clinical worsening in response to anticholinesterase agents have also been reported.[35] Disease onset in patients with anti-MUSK MG tends to be earlier, and patients are predominantly female.[33] Thymus histology is usually normal.[36]

Patients with MG who lack both anti-AChR and anti-MUSK antibodies (so-called seronegative MG) are clinically heterogeneous and can have purely ocular, mild generalised, or severe generalised disease. The true prevalence of seronegative MG might be quite low, because some patients might have low-affinity anti-AChR antibodies that are not detected with currently available assays (see section on immunopathogenesis). Not surprisingly, these patients are essentially indistinguishable from patients with anti-AChR-positive MG in terms of clinical features, pharmacological treatment response, and even thymic abnormalities in some cases.[37]

Myasthenic weakness that remains limited to the ocular muscles is termed ocular MG, and comprises 17% of all MG in white populations.[10] Ocular MG seems to be more common in Asian populations (up to 58% of all patients with MG), with a predilection for children.[11,38] If weakness remains limited to the ocular muscles after 2 years, there is a 90% likelihood that the disease will not generalise.[10] Up to 50% of patients with ocular MG have anti-AChR antibodies, but higher antibody titres do not necessarily predict generalisation.[39] Anti-MUSK antibodies are rarely found in ocular MG.[40–42]

Immunopathogenesis and immunogenetics

The NMJ in MG

The NMJ has three basic components (figure 1): (1) the presynaptic motor nerve terminal, where acetylcholine is synthesised, stored, and released; (2) the synaptic space; and (3) the postsynaptic muscle membrane, which contains the AChRs and the enzyme acetylcholinesterase. Neuromuscular transmission begins when a nerve action potential enters the nerve terminal and triggers the release of acetylcholine. Exocytosis of synaptic vesicles containing acetylcholine requires calcium, which enters the depolarised nerve terminal via voltage-gated Ca^{2+} channels. Acetylcholine diffuses across the synaptic cleft and interacts with the AChRs on the postsynaptic muscle membrane, causing a local depolarisation, the endplate potential (EPP). The EPP in normal NMJs is much larger than the threshold for generation of a muscle fibre action potential; this difference has been defined as the safety factor of neuromuscular transmission. The action of acetylcholine on the postsynaptic membrane is terminated by acetylcholinesterase.

In MG, loss of functional AChRs results in a decrease in EPP amplitudes that fall below the threshold required for muscle fibre action potential generation during repetitive nerve depolarisations, resulting in neuromus cular transmission failure (figure 1).

Anti-AChR MG

The pathogenic role of anti-AChR antibodies in MG has been clearly shown,[2,44,45] and is further substantiated clinically by the often dramatic improvement that follows removal of circulating antibodies by plasma exchange.[46] The antibodies are usually of the IgG1 or IgG3 isotype and are thus capable of activating complement. They bind to the extracellular domain of the AChR molecule, but are heterogeneous in their reactivity with different regions on the AChR.[47] Although antibodies to the AChR directly result in the destruction of the muscle endplate, the high-affinity, highly mutated nature of the anti-AChR IgGs indicates that the autoantibody response is T-cell dependent, with CD4 T cells helping the B cells to produce the pathogenic antibodies.[48–50]

Three main mechanisms underlie the loss of functional AChRs.[51] Perhaps the most important is complement-mediated lysis of the muscle endplate resulting in morphological damage to the postsynaptic muscle membrane.[52] This causes a simplification and distortion of the normal folded pattern of the postsynaptic membrane (figure 1),[43] which not only has a functional impact on AChRs but also results in a reduction in the number of voltage-gated Na^+ channels,

increasing the muscle fibre action potential threshold.[53] Second, accelerated internalisation and degradation of AChRs caused by cross-linkage of AChRs by divalent antibodies results in a temperature-dependent loss of AChRs.[54] Finally, direct blockade of AChRs by antibodies attached to acetylcholine binding sites might be important in some patients.[55]

Early-onset MG

Although the trigger or inciting factor leading to the autoimmune derangement in MG remains a mystery, several lines of evidence implicate the thymus gland in this process. Greater than 80% of early-onset, anti-AChR-positive patients have thymic hyperplasia,[56] characterised by the presence of lymphocytic infiltrates and germinal centres similar to those found in lymph nodes. Hyperplastic thymus glands from patients with MG contain T cells, B cells, and plasma cells, as well as myoid cells that express AChR.[57] In fact, they contain all the components necessary for the development of an immune response to the AChR, and thymocytes in culture spontaneously generate anti-AChR antibodies.[58] These findings support the concept of an intrathymic pathogenesis and suggest that the hyperplastic thymus is involved in the initiation of the anti-AChR immune response in early-onset MG.

Late-onset MG (without thymoma)

The mechanism for autosensitisation to AChRs in late-onset MG is not clear because these patients typically lack thymic abnormalities. The similar clinical presentation and autoantibody profile in some patients with late-onset MG compared with thymomatous MG raises the possibility that they have occult thymomas suppressed by anti-tumour autoimmune reactions.

Thymomatous MG

Thymomas are frequently associated with autoimmunity, probably due to dysregulation of lymphocyte selection and presentation of self-antigens expressed by neoplastic cells. Neoplastic epithelial cells in thymomas express numerous self-like antigens, including AChR-like, titin-like, and ryanodine-receptor-like epitopes.[59] Frequent concurrent autoimmunity against these seemingly unrelated auto antigens in thymomatous MG suggests that their targeted, potentially cross-reacting, proteins play a part in the production of disease.[60] MG-associated thymomas are rich in autoreactive T cells.[61] The current concept of the immunopathogenesis of thymoma-related autoimmunity is that potentially autoreactive T cells are positively selected (for survival) and exported to the periphery where they are activated to provide help for autoantibody-producing B cells by mechanisms that are not yet known. Negative selection and regulation of potentially autoreactive T cells might be impaired in thymoma due to a deficiency in the expression of the autoimmune regulator gene (*AIRE*), and selective loss of T-regulatory cells.[62,63]

Anti-MUSK MG

MUSK is a transmembrane endplate polypeptide involved in a signalling pathway that maintains the normal functional integrity of the NMJ.[64] Recent evidence indicates that anti-MUSK antibodies adversely affect the maintenance of AChR clustering at the muscle endplate, leading to reduced numbers of functional AChRs.[65,66] Furthermore, myasthenic weakness has been reproduced in experimental animals by immunisation with recombinant MUSK ectodomain.[67] MUSK antibodies are mainly IgG4, unlike the IgG1 and IgG3 anti-AChR antibodies, and are not complement activating.[31] The precise pathophysiology of the myasthenic weakness and prominent muscle atrophy in anti-MUSK MG has yet to be elucidated, because muscle biopsy studies have shown little AChR loss,[65] but detailed studies of neuromuscular transmission have not been done in the most affected muscles. The preferential involvement of facial, bulbar, and axial muscles might indicate a different

composition of the NMJs in these muscles. The events leading to autosensitisation to MUSK are not known, but the thymus gland is probably not involved.[36]

Anti-AChR and anti-MUSK-negative MG (seronegative generalised MG)

Patients who do not have either anti-AChR or anti-MUSK antibodies improve with immunosuppressive treatments, plasma exchange, and even thymectomy.[68] Furthermore, muscle biopsies in these patients show AChR loss,[65] and thymic histology often shows hyperplasia and germinal centres similar to anti-AChR-positive MG.[36,69] Recently, low-affinity IgG antibodies that bind preferentially to AChRs clustered on transfected cell surfaces have been found in 66% of patients with MG who were antibody-negative on conventional anti-AChR and anti-MUSK antibody assays.[70] These low-affinity antibodies were mainly of the IgG1 subclass and had the capacity to activate complement, supporting their pathogenic role.

Ocular MG

The immunopathogenesis of ocular MG is likely to be similar to that of early-onset or late-onset generalised MG. Enhanced susceptibility of extraocular muscles to MG might result from differences in NMJ morphology and physiology. Extraocular muscles have less prominent synaptic folds, fewer postsynaptic AChRs and smaller motor units, and are subject to high firing frequencies.[71] Another possibly relevant factor is low expression of complement regulators in extraocular muscles, which might make them more vulnerable to complement-mediated damage.[72,73]

Immunogenetics

The biological and clinical heterogeneity of autoimmune MG seems to correlate with genetic markers, most notably the HLA genes (table 1).[15,74] The most consistent finding is the association of HLA-DR3 and B8 alleles with early-onset MG with thymic hyperplasia.[15,74,75] Late-onset MG is less strongly associated with HLA-DR2 and B7.[76] HLA-DR3 and DR7 seem to have opposing effects on MG phenotype, DR3 having a positive association with early-onset MG and a negative association with late-onset MG (with anti-titin antibodies), and DR7 having the opposite effects.[6] Different HLA associations have been reported in Asian patients with MG with a high frequency of HLA-DR9 in both Chinese and Japanese patients,[77,78] and an association of ocular MG with HLA-BW46 in Chinese patients.[79] No clear genetic links have been found for thymomatous MG, but thymoma patients with particular genetic profiles have a higher risk of developing MG.[80] Recently, an association with DR14-DQ5 has been reported in patients with anti-MUSK antibodies.[81] Anti-MUSK MG is less frequent in some ethnic groups or geographical locations (eg, China, Netherlands), suggesting genetic as well as possibly environmental influences.[11,82]

Several non-HLA genes (*PTPN22*, *FCGR2*, *CHRNA1*) have also been found to be associated with MG; some are also associated with other autoimmune diseases,[76] and might thus represent a non-specific susceptibility to autoimmunity. An exception to this is the *CHRNA1* gene, which encodes the alpha subunit of the AChR and might provide pathogenetic clues specific for MG.

Diagnosis

The tests that are available to confirm the clinical diagnosis of MG include bedside tests, such as the edrophonium or ice-pack test, electrophysiological tests, and tests to measure the concentrations of serum autoantibodies (table 2).

Bedside tests

Edrophonium chloride is a short-acting acetyl-cholinesterase inhibitor that prolongs the duration of action of acetylcholine in the NMJ, increasing the amplitude and duration of the EPP. The edrophonium test, which consists of administering edrophonium intravenously and observation of the patient for an improvement in muscle strength, can be most objectively and reliably interpreted when resolution of eyelid ptosis or improvement in strength of a single paretic extraocular muscle are the endpoints.[83] Published reports indicate that its sensitivity in the diagnosis of MG is 71.5–95% for generalised disease.[83] Serious complications of brady cardia and syncope are rare,[84] but cardiac monitoring during the procedure is advocated by some.[83] The ice-pack test is a non-pharmacological test with no morbidity that is done by placing an ice pack over the eye for 2–5 mins and assessing for improvement in ptosis.[85,86] Its use should mainly be considered in a patient with ptosis in whom the edrophonium test is contraindicated.

Electrophysiological tests

Repetitive nerve stimulation is the most commonly used electrophysiological test of neuromuscular transmission. In disorders of the NMJ, low rates of nerve stimulation (2–5 Hz) produce a progressive decrease or decrement in the amplitude of the compound muscle action potential. The result of the repetitive nerve stimulation test is abnormal in approximately 75% of patients with generalised MG (<50% of ocular MG), and is more likely to be abnormal in a proximal or facial muscle.[86]

Neuromuscular jitter results from fluctuations in the time taken for the EPP to reach the threshold for muscle fibre action potential generation, and can be measured by single-fibre electromyography (SFEMG). SFEMG is done using a specially constructed concentric needle electrode that allows identification of action potentials from individual muscle fibres. SFEMG reveals abnormal jitter in 95–99% of patients with MG if appropriate muscles are examined.[87,88] Jitter can also be assessed, although with somewhat less sensitivity, by using conventional electromyography electrodes.[88–90] Although highly sensitive, increased jitter is not specific for primary NMJ disease, and might be found in nerve or even muscle disease.[86]

Immunological tests

The most commonly used immunological test for the diagnosis of MG measures the amount of serum antibody that precipitates muscle AChR, as detected by binding with the radiolabelled cholinergic antagonist α-bungarotoxin.[91] The sensitivity of this test is approximately 85% for generalised MG and 50% for ocular MG.[91,92] Anti-AChR antibody concentrations vary widely among patients with similar degrees of weakness and thus cannot reliably predict the severity of disease in individual patients. Of note, patients might be falsely seronegative due to immunosuppression or if the test is done too early in the disease.[93] Other assays that measure the capacity of patient serum to inhibit binding of cholinergic ligands (AChR-blocking antibodies) or to induce modulation of AChRs in cell cultures (AChR-modulating antibodies) add relatively little to the diagnostic sensitivity.[94]

Striated muscle (striational) antibodies that recognise muscle cytoplasmic proteins (titin, myosin, actin, and ryanodine receptors) are detected in 75–85% of patients with thymomatous MG and also in some thymoma patients without MG.[20,95] The presence of these antibodies in early-onset MG raises the suspicion of a thymoma. Titin antibodies and other striational antibodies are also found in up to 50% of patients with late-onset, non-thymomatous MG, so are less helpful as predictors of thymoma in patients aged over 50 years.[20,96] Recent reports indicate that anti-KCNA4 antibodies might be a useful marker to identify patients with thymoma and concomitant myocarditis/myositis,[30] but further confirmation is needed.

Patients with generalised MG who are anti-AChR negative should be tested for anti-MUSK antibodies, which are found in approximately 40% of patients in this group.[31] As noted, low-affinity anti-AChR antibodies binding to clustered AChRs have been found in 66% of sera from patients with seronegative generalised MG,[70] but this test is not currently commercially available. Whether low-affinity antibodies are present in ocular MG remains to be determined, but this cell-based assay might eventually provide a more sensitive diagnostic test in this subgroup.

Diagnostic testing strategy and miscellaneous tests

Testing for anti-AChR antibodies should be done in all patients with suspected MG. In practice, bedside and electrophysiological tests are commonly done concurrently with antibody testing because the results of the latter are usually delayed. The testing sequence (figure 2) depends on clinical presentation and the available expertise (eg, SFEMG). The differential diagnoses of MG are given in table 3. Disorders such as chronic fatigue syndrome and certain mood disorders can usually be distinguished from MG by symptoms of generalised exhaustion, malaise, and apathy, for example, rather than true fatigable muscle weakness.

Chest CT or MRI is done in all patients with confirmed MG to exclude the presence of a thymoma. Iodinated contrast agents should be used with caution because they might exacerbate myasthenic weakness.[97,98] MG often coexists with thyroid disease, so baseline testing of thyroid function should be obtained at the time of diagnosis. In anticipation of immunosuppressive treatment, screening for tuberculosis is desirable.

Treatment and management

Cholinesterase inhibitors

Oral cholinesterase inhibitors increase the amount of acetylcholine available for binding in the NMJ, and are the first-line treatment in patients with MG (table 4).[1] Pyridostigmine bromide is the most commonly used cholinesterase inhibitor. The initial oral dose in adults is 15–30 mg every 4–6 h, which is increased and adjusted to maximise benefit and minimise side-effects (diarrhoea, stomach cramps). Pyridostigmine can be given 30–60 mins before meals in patients with bulbar symptoms. Cholinesterase inhibitors rarely induce complete or sustained relief of MG symptoms and do not affect disease progression, but might be sufficient for adequate management in certain patients with non-progressive mild or purely ocular disease. Doses of pyridostigmine exceeding 450 mg daily (or even lower in patients with renal failure[133]) can induce worsening muscle weakness due to depolarisation block of neuromuscular transmission. Cholinergic overdose is often (but not always) accompanied by the muscarinic symptoms of hyper salivation, bradycardia, hyperhidrosis, lacrimation, and miosis.

Short-term immune therapies

Plasma exchange and intravenous immunoglobulin are used for short-term treatment of MG exacerbations and when it is desirable to achieve a rapid clinical response (table 4). Plasma exchange temporarily reduces the concentrations of circulating anti-AChR antibodies and produces improvement in a matter of days in most patients with acquired MG.[46,100] Typically one exchange, removing one to two plasma volumes, is done every other day, up to a total of four to six times. Published reports indicate that plasma exchange effectively improves strength in most patients with severe MG.[46,100–102] Common side-effects include hypotension and paresthesias from citrate-induced hypocalcaemia. Infections and thrombotic complications related to venous access have been reported.[101,102] Plasma exchange can also reduce coagulation factors, particularly with repeated treatments, leading to bleeding tendencies.[102] Circulating anti-AChR pathogenic factors can also be removed using immunoadsorption columns, some of which use immobilised AChR as an immunoadsorbent.[105–107] Continued

development of this technique might provide a more efficient and safer alternative to plasma exchange.

Intravenous immunoglobulin is widely used for patients with exacerbating MG. Support for its use comes from randomised controlled trials that show efficacy similar to plasma exchange,[134] equal efficacy of two doses (1 g/kg *vs* 2 g/kg),[103] and a recent double-blind, placebo-controlled trial in patients with MG with worsening weakness.[104] The mechanisms by which intravenous immunoglobulin produce improvement are not clear, but two important possibilities are competition with autoantibodies and Fc-receptor binding.[135] The standard dosing regimen for intravenous immunoglobulin (1–2 g/kg) involves the infusion of large volumes and is very expensive. Although rare, severe complications do occur, some of which are related to the large volume and high viscosity of the infused preparation.[136]

Long-term immune therapies

Most therapeutic recommendations on the use of chronic immunosuppressive agents for MG are based on evidence from either small, randomised controlled trials, or anecdotal experience based on uncontrolled observations (table 4). There are major limitations inherent in the design of clinical trials in rare disorders such as MG. The commonly used immunosuppressant treatments for MG are described with recommendations based on the best available information.

Corticosteroids—Corticosteroids were the first immunosuppressant medications to be used in MG, and remain the most commonly used immune-directed therapy.[99] In four large retrospective series of steroid treatment for generalised MG, administered at various doses, more than 73% of the 422 patients treated achieved either marked improvement or remission.[108–111] Prednisone is generally used when symptoms of MG are not adequately controlled by cholinesterase inhibitors alone.[99] It can be administered at high doses (0.75–1.0 mg/kg daily) initially, and then gradually tapered off or continued at low doses for many years. Approximately a third of patients have a temporary exacerbation after starting prednisone; this usually begins within the first 7–10 days with high prednisone doses and lasts for several days.[108,111] In mild cases, cholinesterase inhibitors are usually used to manage this worsening. In patients with oropharyngeal or respiratory involvement, plasma exchange or intravenous immunoglobulin can be given before beginning prednisone to prevent or reduce the severity of corticosteroid-induced exacerbations and to induce a more rapid response. Once improvement begins, subsequent corticosteroid-induced exacerbations are unusual.

Some clinicians prefer to begin prednisone with a low dose (10–25 mg) and gradually increase to 60–100 mg on alternate days.[137,138] The dose is maintained until maximum improvement is reached, and then the dose is tapered as above. Exacerbations might still occur with this approach, but the onset of such worsening and the therapeutic responses are less predictable. Whereas corticosteroids are highly effective in MG, they usually must be given chronically, with significant risk for adverse events (table 5).[139]

Oral prednisone at relatively low doses (20 mg/day, increased by 5–10 mg/day every 3 days until symptoms resolve) might be more effective than anticholinesterase drugs in ocular MG (table 4, figure 3).[140,141] Prednisone should therefore be considered in all patients with ocular MG who do not achieve full control of symptoms with anticholinesterase medications. Although not definitive, evidence suggests that corticosteroid treatment might delay or reduce the frequency of progression of ocular MG to generalised disease.[39]

Non-steroidal immunosuppressive agents—Azathioprine is a purine antimetabolite that interferes with T-cell and B-cell proliferation. Retrospective studies indicate that azathioprine is effective in 70–90% of patients with MG, but the onset of benefit might be

delayed for as long as 12 months.[112–114] Azathioprine (initiated at 50 mg daily) can be used alone or as a steroid-sparing agent in MG, but when used in combination with prednisone it might be more effective and better tolerated than prednisone alone.[115] In the absence of systemic side-effects, the dose is then gradually titrated upward by 50 mg per week to a daily dose of 2–3 mg/kg. In 15–20% of patients, an idiosyncratic reaction with influenza-like symptoms, which requires the drug to be stopped, occurs within 10–14 days after starting azathioprine. Hepatotoxicity and leukopenia are also important adverse effects,[142] but are reversible if detected early and the dose of azathioprine is reduced or discontinued. Patients with thiopurine methyl transferase deficiency cannot completely metabolise azathioprine, and a normal dose might lead to dangerous leukopenia.[143] Measurement of thiopurine methyl transferase concentrations is recommended before initiating azathioprine therapy, and is certainly advisable with early or marked azathioprine-associated leukopenia. Long-term use of azathioprine might increase the risk of developing certain malignancies.[144] This risk is probably dose and duration dependent, so the minimum effective maintenance dose of azathioprine should be used.

Mycophenolate mofetil selectively blocks purine synthesis, thereby suppressing both T-cell and B-cell proliferation. Clinical efficacy in MG has been suggested by case series,[116,117] and in a retrospective analysis of 85 patients with MG.[118] The standard dose used in MG is 1000 mg twice daily, but doses up to 3000 mg can be used. Higher doses are associated with myelosuppression, and complete blood counts should be monitored at least monthly. Two recently completed controlled trials of mycophenolate mofetil in MG failed to show additional benefit over 20 mg daily prednisone given as initial immunotherapy,[119] or a significant steroid-sparing effect in patients on prednisone.[120] Several factors have been cited to explain these negative results, including the generally mild disease status of the patients, the better-than-expected response to relatively low-dose prednisone, and the short duration of the studies.[145] Although the clinical efficacy of mycophenolate mofetil in MG remains an open question, it continues to be widely used in the treatment of MG.

Ciclosporin inhibits T-cell proliferation via disruption of calcineurin signalling, which blocks the synthesis of interleukin 2 and other proteins essential to the function of CD4 T cells. Its efficacy in MG has been suggested by a small, randomised, placebo-controlled clinical trial, [121] and retrospective studies have supported its use as a steroid-sparing agent.[122] Ciclosporin is used mainly in patients in whom azathioprine is either ineffective or not tolerated. The recommended initial daily dose of ciclosporin is 4–6 mg/kg in two divided doses, but maintenance daily doses of 3–4 mg/kg or less are often adequate to maintain the effect. Side-effects are common and include hirsutism, tremor, gum hyperplasia, and anaemia, but hypertension and nephrotoxicity are the main treatment-limiting adverse reactions.[122]

Tacrolimus (FK506) has a similar mechanism of action as ciclosporin, and potential benefit in MG has been suggested by several reports,[123–125] including a randomised, but unblinded, study in 36 patients with de novo MG.[125] Sustained benefit has been reported in anti-ryanodine-receptor-positive patients, which has been hypothesised to be due to enhancement of ryanodine-receptor-related sarcoplasmic calcium release.[126] Daily doses of 3–5 mg have been used in different series, with a side-effect profile suggesting that it is less nephrotoxic than ciclosporin.

Other immunosuppressive agents—A small percentage of patients with MG are refractory or develop intolerable side-effects to treatment with corticosteroids in combination with one or more of the immunosuppressive agents described above. Agents that can be considered in these refractory patients include cyclophosphamide and rituximab.

In a recent randomised controlled trial, pulsed doses of intravenous cyclophosphamide (500 mg/m^2) given to patients with refractory MG improved muscle strength and reduced steroid requirement.[127] Remarkable therapeutic responses have also been reported in patients with refractory MG receiving a one-time, high-dose (50 mg/kg) intravenous course of cyclophosphamide for 4 days followed by rescue therapy, with benefit persisting for several years without relapse.[128,129] Side-effects of cyclophosphamide are common and potentially serious, and include myelosuppression, haemorrhagic cystitis, and an increased risk for infection and malignancy.[146]

Rituximab is a chimeric monoclonal antibody directed against the B-cell surface marker CD20. It effectively reduces circulating B-cell counts, and on the basis of its potential for targeting autoreactive B-cell clones, might have a therapeutic role in antibody-mediated autoimmune diseases. Several case reports have suggested benefit in patients with refractory MG and in those with MUSK MG.[130–132] Further investigation is needed to determine its role in MG therapy.

Thymectomy—The use of thymectomy in MG was initially based on empirical observations that patients with MG improved after removal of the thymus.[147] The presumed role of the thymus in MG has provided theoretical justification for the procedure, and thymectomy has been used as a treatment for non-thymomatous MG for nearly 70 years. There have been no randomised controlled trials, and conclusions from retrospective, non-randomised studies are confounded by baseline differences between surgical and non-surgical groups, among other things. A comprehensive meta-analysis concluded that there was probably some benefit from thymectomy, and that it should be considered as a treatment option in selected patients with MG.[148] Most experts consider thymectomy to be a therapeutic option in anti-AChR-positive, generalised MG with disease onset before the age of 50 years, and some would also recommend it in patients who lack anti-AChR antibodies. An international, prospective, single-blinded randomised trial of thymectomy in non-thymomatous MG is currently ongoing, and will hopefully clarify this issue. At this time, the only absolute indication for thymectomy is the presence of thymoma. The role of thymectomy in anti-MUSK MG is not clear.[33,149]

Management principles

The treatment of patients with MG (figure 4) must be individualised according to clinical presentation or subtype, and requires comprehensive assessment of the patient's functional impairment and its effect on daily life. The therapeutic goal is to return the patient to normal function as rapidly as possible while minimising the side-effects of therapy. Cholinesterase inhibitors might be sufficient in some patients with ocular MG or mild generalised disease (with or without prior thymectomy). In patients treated with immunotherapies, the lowest effective dose should always be determined. Long-term risks of infections and malignancy are not clearly defined, but opportunistic infections and malignancies have been associated with the immuno-suppressants commonly used in MG.[150,151] It is important to ensure that patients are also aware of medications that might exacerbate MG symptoms (panel 2). Recently, exacerbations of MG have been reported in patients taking statins.[152] The causal relationship in these cases might be questionable given the widespread use of these agents, but statins should probably be withdrawn if MG worsens with therapy.

Panel 2: **Medications that might exacerbate MG**

Contraindicated

- D-penicillamine

Use with great caution

- Telithromycin (use only if no other option is available)

Will exacerbate weakness in most patients with MG

- Curare and related drugs
- Botulinum toxin
- Aminoglycosides (gentamycin, kanamycin, neomycin, streptomycin, tobramycin)
- Macrolides (erythromycin, azithromycin)
- Fluoroquinolones (ciprofloxacin, levofloxacin, norfloxacin)
- Quinine, quinidine, procainamide
- Interferon-alfa
- Magnesium salts (intravenous magnesium replacement)

Might exacerbate weakness in some patients with MG

- Calcium channel blockers
- Beta-blockers
- Lithium
- Iodinated contrast agents
- Statins (causal relationship in these cases might be questionable given the widespread use of these agents)

MG=myasthenia gravis.

Search strategy and criteria

References for this Review were identified through searches of Medline and PubMed for articles from 1966 to February, 2009, by use of the search terms “myasthenia gravis” and “autoimmune myasthenia”. Articles were also identified through searches of the authors’ own files. Only papers published in English were reviewed.

Myasthenic crisis

The classic definition of myasthenic crisis is weakness from MG that is severe enough to necessitate intubation for ventilatory support or airway protection.[153] Intubation is generally indicated if there is evidence of respiratory muscle fatigue with increasing tachypnea and declining tidal volumes, hypoxaemia, hypercapnea, and difficulty handling secretions. Recommended practice is to discontinue the use of cholinesterase inhibitors after intubation because they might complicate the management of airway secretions and are not needed to support vital functions. Because of its rapid onset of action, plasma exchange is the favoured treatment for myasthenic crisis. Comparison studies suggesting that intravenous immunoglobulin is similarly efficacious in myasthenic crisis generally used suboptimum plasma exchange regimens and did not compare the onset of response.[134] Other reports suggest that intravenous immunoglobulin might be less effective than plasma exchange.[154] Because the effect of plasma exchange is only temporary, longer-acting immune-directed treatments (usually high-dose daily prednisone) should be added to maintain a longer therapeutic effect.

The timing of extubation and factors predicting success are not well established, but one report indicates that atelectasis is the strongest predictor of the need for reintubation.[155] Non-invasive mechanical ventilation using bilevel positive-pressure ventilation might reduce the need for

intubation in myasthenic patients who have not developed hypercapnea (partial CO_2 pressure >50 mm Hg).[156,157]

Transient neonatal myasthenia

Muscle weakness due to transplacental passage of maternal pathogenic autoantibodies is termed transient neonatal myasthenia and occurs in approximately 10–15% of infants born to mothers with MG.[18] Symptoms usually develop a few hours after birth, but might be delayed for 24 h or longer, requiring sustained vigilance by the treating physician. Rarely, weakness manifests in utero, particularly if maternal antibodies are directed against fetal AChR, and can lead to arthrogryposis multiplex congenita.[158] Prophylactic treatment with plasma exchange or steroids, or both, can be considered in a woman with a previously affected child, as the risk of recurrent transient neonatal myasthenia is high.

Conclusions and future challenges

There are several emerging therapies for MG, including tacrolimus, rituximab, and antigen-specific apheresis, whereas other treatments await clarification of efficacy and their role in MG (thymectomy, mycophenolate mofetil). In addition, the soluble tumour-necrosis-factor-receptor blocker, etanercept, has been used with some success as a steroid-sparing agent in small numbers of patients with MG, but further study is needed because disease worsening was observed in some patients.[159] Preliminary studies of an antisense oligonoucleotide (EN101) that blocks the expression of a splice isoform of acetylcholinesterase have been recently published.[160] Oral administration of EN101 produced marked improvement in MG symptoms and seemed to be safe and well tolerated, with minimum cholinergic side-effects. Clinical trials of EN101 are ongoing.

Complement inhibitory therapy has been shown to be effective in experimental MG,[161] and might hold promise in myasthenic crisis and particularly in ocular MG because of the low expression of complement regulators in extraocular muscle.[72,73] Preliminary clinical trials in human myasthenia are being organised.

Obviously, the ideal therapy for MG would eliminate or suppress the specific autoimmune response without otherwise affecting the immune system. Unfortunately, current evidence indicates that the autoimmune T-cell and antibody responses in MG are highly heterogeneous,[162,163] making this a challenging approach, and suggesting that harnessing or facilitating the immune system's regulatory network might be an effective strategy. Approaches along these lines that have been successful in experimental MG include the induction of tolerance to AChR peptide and the use of altered antigenic peptides.[164–166] The manipulation of antigen-presenting cells (dendritic cells) and the mobilisation of regulatory T cells have also been recently reported to be effective in both the suppression of induction and treatment of experimental MG.[167–169] Recent findings that B cells have critical positive and negative roles in autoimmune disease might lead to particularly effective therapeutic strategies that specifically target anti-AChR antibody-producing B cells.[170]

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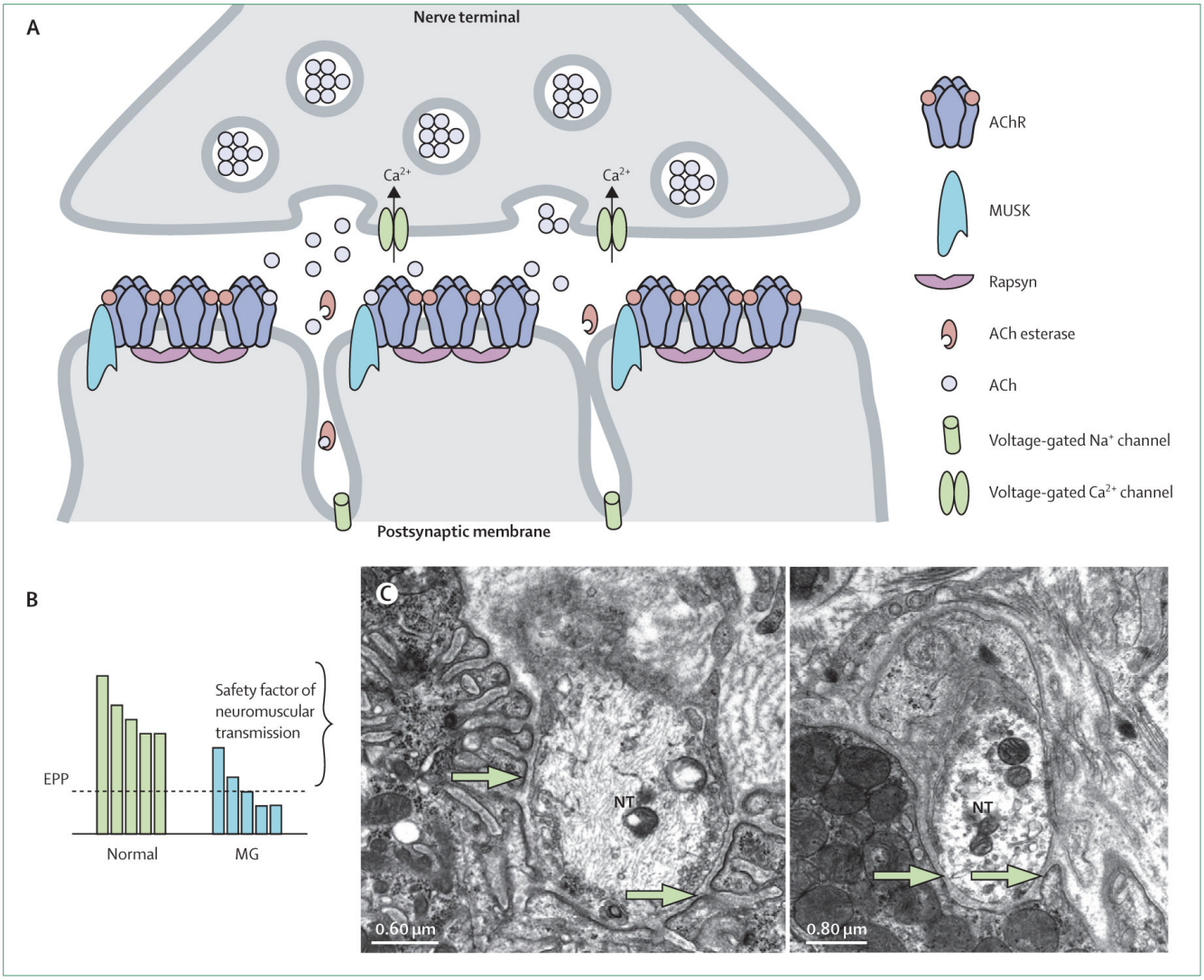

Figure 1. The normal NMJ and pathophysiology of MG

(A) Components of the NMJ. In the normal NMJ, ACh is released from the nerve terminal following a nerve action potential, and interacts with the AChR on the postsynaptic membrane. Voltage-gated Ca^{2+} channels allow the influx of Ca^{2+} into the nerve terminal, which facilitates the release of ACh. Voltage-gated Na^{+} channels on the postsynaptic membrane serve to propagate the muscle action potential on depolarisation. Acetylcholinesterase scavenges and hydrolyses unbound ACh. MUSK initiates clustering of the cytoplasmic protein rapsyn and AChRs, and is believed to maintain normal postsynaptic architecture. (B) Effect of the loss of functional AChRs in MG. Conceptual representation of EPP amplitudes after repeated nerve stimulation. EPP amplitude is reduced in MG, narrowing the safety factor of neuromuscular transmission. With repeated stimulations, the EPP amplitude falls below threshold (indicated by the dotted line) for muscle fibre activation, resulting in neuromuscular transmission failure. (C) Electron micrographs of endplate regions from mice with experimental MG, showing lysis and altered morphology of the postsynaptic membrane. A normal endplate region is shown in the left panel. An endplate region from a myasthenic mouse showing loss of normal endplate morphology due to complement-mediated lysis is shown in the right panel. Postsynaptic membranes are indicated by the arrows. ACh=acetylcholine. AChR=ACh receptor.

EPP=endplate potential. MG=myasthenia gravis. MUSK=muscle-specific receptor tyrosine kinase. NMJ=neuromuscular junction. NT=nerve terminal. Panel C modified with permission from Lippincott Williams & Wilkins.[43]

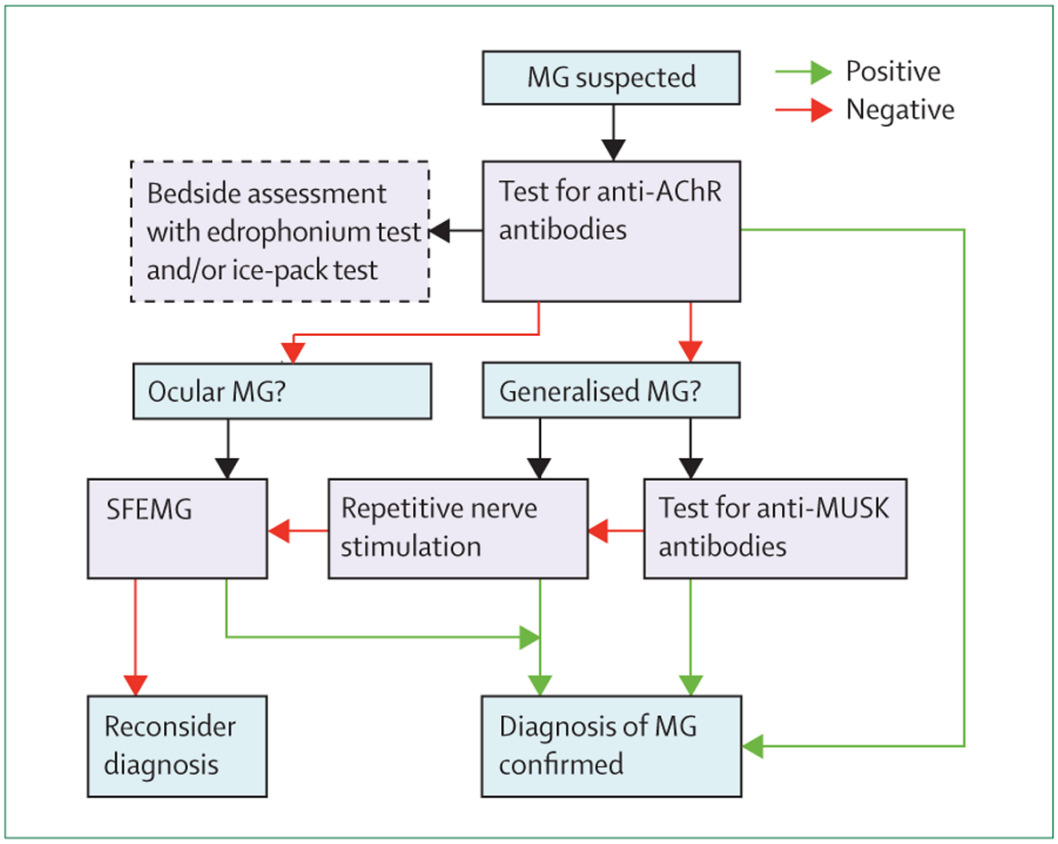

Figure 2. Diagnostic flowchart

All patients with suspected MG should undergo testing for anti-AChR antibodies. The detection of serum anti-AChR antibodies in a patient with the appropriate clinical presentation essentially confirms the diagnosis of MG, and obviates the need for further testing. Anti-MUSK testing is usually done on patients with generalised MG who are negative for AChR antibodies, but consideration might be given to initial anti-MUSK testing (at the time of anti-AChR testing) in the presence of severe bulbar and facial weakness with marked muscle atrophy. The repetitive nerve stimulation and SFEMG tests are usually done while the results of the antibody tests are awaited; even if electrophysiological tests are positive, the results of antibody tests are still useful to identify patients with particular subsets of MG. The edrophonium and ice-pack tests are used in selected patients to make a bedside confirmation of a suspected diagnosis of MG (indicated by a dashed outline), but more objective confirmation is desirable (anti-AChR antibodies, repetitive nerve stimulation, or SFEMG). AChR=acetylcholine receptor. MG=myasthenia gravis. MUSK=muscle-specific receptor tyrosine kinase. SFEMG=single-fibre electromyography.

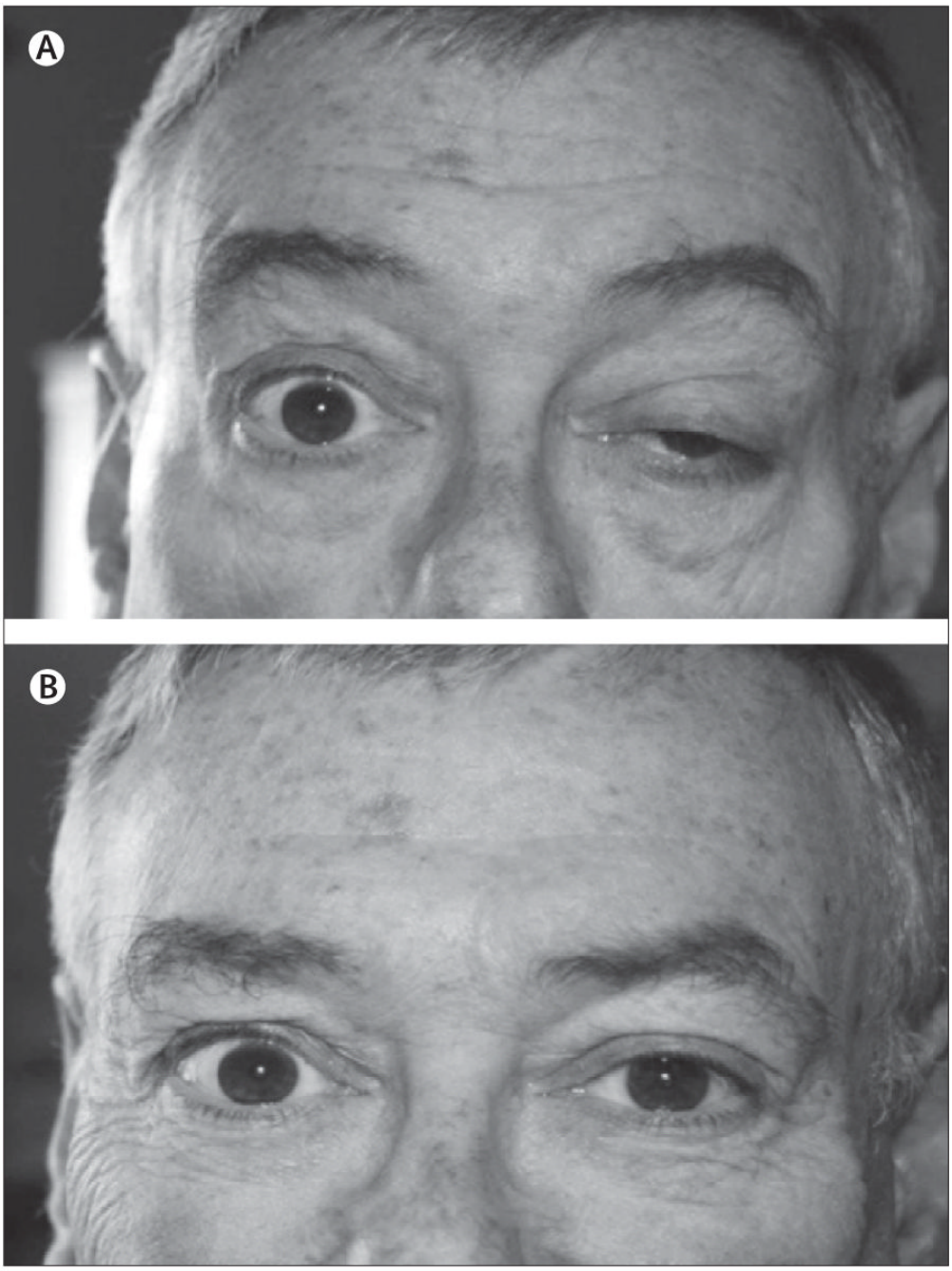

Figure 3. Response of ocular myasthenia gravis to moderate dose daily prednisone

(A) Before treatment, obvious left ptosis and prominent symptoms of diplopia, which did not fully respond to treatment with pyridostigmine. (B) 13 days after initiation of prednisone 30 mg daily. Patient is now asymptomatic with marked improvement in left ptosis.

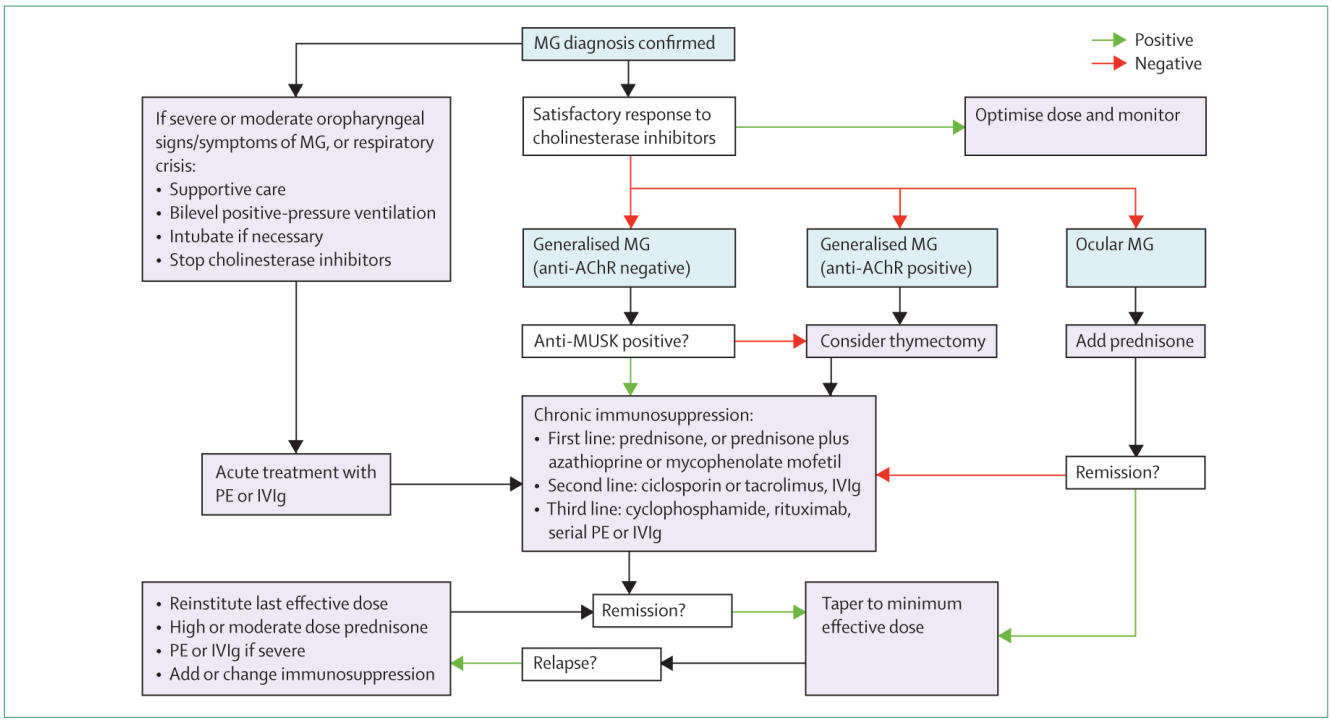

Figure 4. Treatment flowchart

Management of MG must be individualised, but this general approach is suitable for most patients. Thymectomy is usually considered in early-onset, anti-AChR-positive MG. Pre-operative immunosuppression (PE or IVIg with or without steroids) might be required, particularly in patients with oropharyngeal or respiratory weakness, but some patients can successfully undergo thymectomy without prior treatment. If a thymoma is discovered, thymothymectomy is a requisite component of early disease management. A course of PE/IVIg can be considered at initiation of chronic immunosuppression to hasten onset of clinical response. AChR=acetylcholine receptor. IVIg=intravenous immunoglobulin. MG=myasthenia gravis. MUSK=muscle-specific receptor tyrosine kinase. PE=plasma exchange.

Table 1

Clinical subtypes of myasthenia gravis

	Age at onset (years)	Thymic histology	Muscle autoantibodies	HLA associations	Comments
Early onset	<40	Hyperplasia	AChR	DR3-B8, DR9 (in Asians)	Male:female ratio=1:3
Late onset	>40	Normal	AChR, titin, ryanodine receptor	DR2-B7	Anti-titin and ryanodine-receptor antibodies associated with severe disease
Thymoma	40–60 (usually)	Neoplasia	AChR, titin, ryanodine receptor, KCNA4	None identified	Might be associated with other paraneoplastic disorders
MUSK	<40 (most patients)	Normal	MUSK	DR14-DQ5	Marked female predominance; selective oropharyngeal, facial, respiratory weakness in some patients
Seronegative (generalised)	Variable	Hyperplasia in some	Antibodies against clustered AChR in 66%	None identified	Unidentified autoantigen in those without low-affinity antibodies?
Ocular	Adult in USA and Europe; childhood in Asia	Unknown	AChR in 50%	Bw46 (in Chinese patients)	Low-affinity AChR antibodies?

AChR=acetylcholine receptor. KCNA4=voltage-gated K^+ channel subfamily A member 4. MUSK=muscle-specific receptor tyrosine kinase.

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Table 2

Diagnostic tests for MG

	Details
Bedside	
Edrophonium test	Reliable in patients with ptosis/extraocular weakness
Ice-pack test	Used only when assessing improvement in ptosis
Electrophysiological	
Repetitive nerve stimulation	75% of generalised MG, <50% of ocular MG
Single-fibre electromyography	Highly sensitive (95–99%), but not specific
Immunological (autoantibodies)	
Anti-AChR (binding)	85% of generalised MG, 50% of ocular MG
Anti-MUSK	40% of AChR-negative generalised MG
Low-affinity anti-AChR	66% of AChR and MUSK-negative generalised MG
Anti-titin	95% of thymomatous MG, 50% of late-onset, non-thymomatous MG
Anti-ryanodine receptor	70% of thymomatous MG (more severe disease)
Other	
CT scan or MRI of chest	Obtain in all patients after diagnostic confirmation of MG
Thyroid function testing	..

AChR=acetylcholine receptor. MG=myasthenia gravis. MUSK=muscle-specific receptor tyrosine kinase.

Table 3

Differential diagnoses of myasthenia gravis

	Differentiating points
Lambert-Eaton myasthenic syndrome	Relative sparing of ocular muscles; hyporeflexia, autonomic features (dry mouth, impotence, postural hypotension)
Congenital myasthenic syndromes	Seronegative; onset in infancy or childhood; no response to immunomodulatory therapy
Botulism	Rapid descending pattern of progression; pupillary, autonomic involvement
Motor neuron disease	Presence of corticobulbar features, muscle cramps/fasciculations/atrophy, upper motor neuron signs
Mitochondrial disorders	Onset more gradual; no fluctuation; symmetric weakness; often no diplopia despite severe ophthalmoplegia
Acute inflammatory demyelinating polyneuropathy variant syndromes	No fluctuation in weakness; areflexia; acute onset
Thyroid ophthalmopathy	Proptosis
CNS disorders causing cranial nerve dysfunction	Sudden onset; consciousness, coordination, and sensation affected; ocular weakness in distribution of individual nerves

Table 4

Treatment options and management of MG

	Initial dosing and frequency	Comments
Symptomatic therapy		
Pyridostigmine[1,99]	30–90 mg every 4–6 h	Causes worsening in some MUSK MG patients
Short-term immune therapies		
Plasma exchange[100–102]	4–6 exchanges on alternate days	Treatment of choice in myasthenic crisis
Intravenous immunoglobulin[103,104]	1–2 g/kg (over 2–5 days)	Use in patients with exacerbating MG
AChR immunoadsorption[105–107]	Not established	Might offer more efficient/safer alternative to plasma exchange
Long-term immune therapies		
Prednisone[108–111]	0.75–1.0 mg/kg daily; or 60–100 mg on alternate days (gradual escalation); or 20–40 mg daily for ocular MG	First-line immune therapy; short-term use of high doses; frequent side-effects
Azathioprine[112–115]	2–3 mg/kg daily	First-line steroid-sparing
Mycophenolate mofetil[116–120]	2–2.5 g daily in divided twice daily doses	First-line steroid-sparing? Widely used in USA
Ciclosporin[121,122]	4–6 mg/kg daily in divided twice daily doses	Steroid-sparing in patients intolerant of or unresponsive to azathioprine or mycophenolate mofetil
Tacrolimus[123–126]	3–5 mg daily	Steroid-sparing in patients intolerant of or unresponsive to azathioprine, mycophenolate mofetil, or ciclosporin
Cyclophosphamide[127–129]	500 mg/m^2 or 4×50 mg/kg	Use in refractory/severe MG
Rituximab[130–132]	2×1000 mg intravenously (separated by 2 weeks)	Use in refractory/severe MG

AChR=acetylcholine receptor. MG=myasthenia gravis. MUSK=muscle-specific receptor tyrosine kinase.

Table 5

Adverse events related to treatment of myasthenia gravis with corticosteroids

	Strategies for prevention
Sodium/fluid retention	Sodium-restricted diet
Obesity	Low-calorie, low-fat diet; exercise
Potassium loss	Supplement as needed
Hypertension	Monthly checks with treatment as necessary
Impaired glucose tolerance	Monitor fasting blood glucose and treat if necessary
Osteoporosis	Bisphosphonates, calcium plus vitamin D, bone-density measurements, female hormone replacement therapy
Psychosis/anxiety	Anxiolytics, antidepressants, use minimum effective steroid dose
Cataracts/glaucoma	At least yearly ophthalmological assessment
Steroid myopathy	Exercise, high-protein diet
Growth suppression (children)	Use minimum effective dose
Peptic ulcer disease	Histamine H_2 receptor antagonists, proton-pump inhibitors