

# An update on myasthenia gravis

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## Summary

*Myasthenia gravis (MG) is an autoimmune disease characterised by autoantibodies against acetylcholine receptors at neuromuscular junctions, resulting in defective neuromuscular transmission. The characteristic features are fatigability and fluctuating weakness of skeletal muscles. It commonly presents with diplopia or unilateral ptosis, which are worse in the evenings. Respiratory muscle weakness may result in respiratory failure. MG is associated with various autoimmune diseases, and thymic hyperplasia or thymoma. An early diagnosis depends on a high index of suspicion, and is confirmed using tensilon test, and electromyography (EMG), and by a raised acetylcholine receptor antibody titre. Symptomatic treatment consists of cholinesterase inhibitors, corticosteroids and other immunosuppressants. Plasmapheresis or pooled intravenous human IgG (IVIgG) provides rapid but short-term relief for acute exacerbations. Thymectomy provides long-term control for patients with thymic hyperplasia, and is essential for thymomas.*

## 摘要

重症肌無力是一種自身免疫疾病，是由於自身抗體破壞神經肌聯接處乙酰膽碱受體所致。重症肌無力的特點是疲勞和肌肉衰弱，常見的病徵包括複視和單側眼皮下垂；其病徵波動不定，在黃昏時間比較明顯。呼吸肌肉軟弱可以引起呼吸衰竭。重症肌無力和其他自身免疫疾病有關，胸腺增生和胸腺瘤是常見的聯合病變。高度的警覺性是及早診斷此病的基礎。診斷劑測試、肌電圖和乙酰膽碱受體抗體滴度增高都對診斷有幫助。乙酰膽碱酯酶抑制劑、激素和免疫抑制藥物可幫助控制病徵。血漿除去術或使用人體免疫球蛋白可以為急性惡化的病人提供迅速但短暫的病情改

善。而胸腺切除手術更可帶來長遠的病情控制；所有患胸腺瘤的病人，胸腺切除手術是必須的。

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## Introduction

Myasthenia gravis (MG) is an acquired autoimmune neuromuscular junction (NMJ) disorder of skeletal muscles. It is characterised by the presence of autoantibodies that bind to acetylcholine receptors (AChR) at the postsynaptic membrane. Such autoantigen-autoantibody interaction leads to the destruction of nicotinic AChR at the NMJ. Congenital myasthenia gravis is pathophysiologically different, caused by a non-immunological abnormality of neuromuscular transmission. This following article will focus on acquired MG only.

## Clinical features

The characteristic clinical features are fatigability and fluctuating weakness of skeletal muscles. The weakness can affect any voluntary muscles. The commonly affected muscles are the levator palpebrae, extraocular muscles, bulbar, facial, neck, limb and trunk muscles. Respiratory muscles are usually involved in severe MG and may lead to potentially life-threatening respiratory failure. The most common presenting symptoms are diplopia or unilateral ptosis that occurs in about 50% of patients. Symptoms usually appear towards the end of the day. The common clinical features are listed in **Table 1**. Occasionally, the first symptom may be weakness of finger or foot extensors, noticed, for example, during piano playing and jogging. Rarely, it may be diagnosed after prolonged postoperative apnoea following the use of muscle relaxants. Precipitating factors may include stress, infections, certain medications, such as aminoglycosides and neuromuscular blockers such as suxamethonium and atracurium, and in women, menstruation<sup>1</sup> and puerperium.<sup>2</sup>

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**Table 1: Clinical features of myasthenia gravis**

- 1) Fatigability
- 2) Fluctuating weakness of skeletal muscles — facial, neck, limb, trunk
- 3) Eye signs — variable ptosis, ophthalmoplegia, diplopia
- 4) Bulbar weakness — dysarthria, dysphagia, weakness of mastication, nasal speech
- 5) Respiratory muscle weakness — respiratory distress, respiratory failure
- 6) Prolonged apnoea after use of muscle relaxants
- 7) Localised muscle atrophy in a small proportion of patients

### Epidemiology

The prevalence of MG in Hong Kong Chinese is about 60 per million and the incidence is about four per million of population/year,<sup>3</sup> compared to a prevalence of 32 to 90 per million population, and an incidence of two to six per million population/year in Japanese and Caucasians.<sup>4,6</sup> Women are affected twice as often as men, but no significant gender difference in incidence exists before puberty, or after the age 40 years.<sup>3,5,6</sup> About 33% of Chinese adult-onset patients have ocular MG. About 30% of MG patients have mild disease, 25% have moderately severe involvement, 12% have fulminant disease and 1.3% have late severe disease. The mean age at onset of symptoms in Hong Kong Chinese patients is about 35 years.<sup>7</sup> Chinese patients have a higher incidence of ocular MG than Caucasians; 33% versus 13-20%.<sup>1</sup>

### Associated autoimmune diseases

MG is associated with a number of autoimmune diseases (**Table 2**). The most common association is with thyroid diseases (usually hyperthyroidism due to thyroiditis). Some features in MG patients may be due to the associated disease or its treatment rather than MG per se. For example, muscle weakness may be due to thyroid dysfunction. Ophthalmoplegia may be a feature of Graves' disease. Rheumatoid arthritis patients treated with penicillamine may develop drug-induced MG.<sup>8</sup>

### Pathophysiology

The endplate contains 10 to 20 million AChR that are densely packed at the interjunctional folds. (**Figure 1**).

AChR in a normal endplate is composed of five subunits made up of four types of peptide chains —  $\alpha$ ,  $\beta$ ,  $\delta$  and  $\epsilon$ .<sup>10</sup> Although most AChR antibodies are directed at sequences of the  $\alpha$  chain, they may bind to all the peptide chains of the AChR. They damage AChR via complement-mediated lysis,<sup>11</sup> and by crosslinking the receptors.<sup>12</sup> The number and density of AChR are reduced,<sup>13</sup> resulting in smaller EPP amplitudes and thus, defective neuromuscular transmission.

### Thymic abnormalities in MG

Thymic hyperplasia is found in more than 70% of patients.<sup>14</sup> About 15% of MG patients have a thymoma.<sup>1</sup> In general, MG patients with thymoma have more severe symptoms, and are more likely to be associated with autoimmune diseases and extrathymic malignancies.

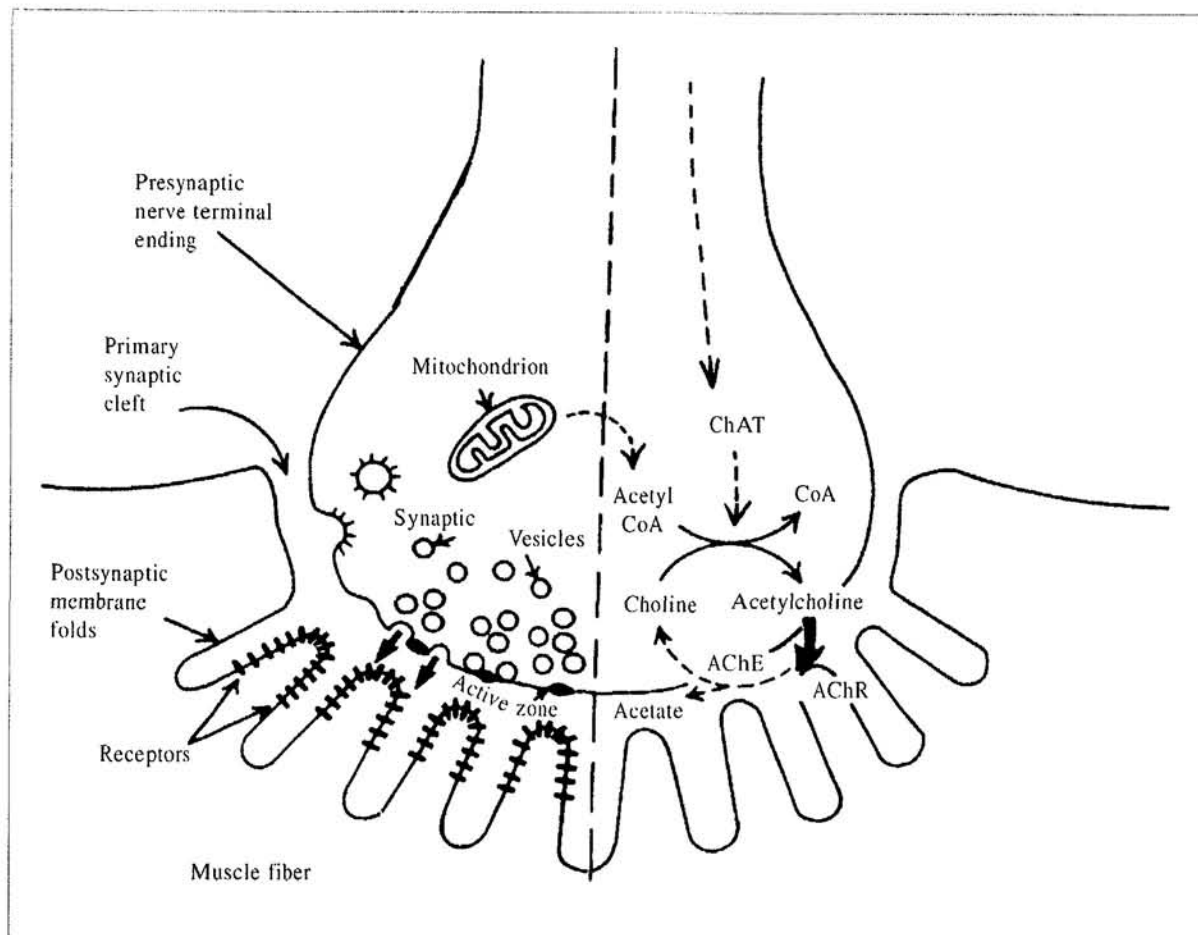
### Diagnosis

The diagnosis of MG is based on clinical features, and appropriate investigations (**Table 3**).

**Table 2: Autoimmune diseases associated with myasthenia gravis**

- 1) Thyroid diseases
- 2) Rheumatoid arthritis
- 3) Systemic lupus erythematosus
- 4) Scleroderma
- 5) Polymyositis
- 6) Sjogren's syndrome
- 7) Glomerulonephritis
- 8) Autoimmune adrenalitis
- 9) Pernicious anaemia
- 10) Autoimmune thrombocytopenia
- 11) Haemolytic anaemia
- 12) Pure red cell anaemia, pancytopenia (almost exclusively related to thymoma)
- 13) Ulcerative colitis, Crohn's disease
- 14) Sarcoidosis
- 15) Primary ovarian failure
- 16) Pemphigus

Figure 1: Schematic diagram of the neuromuscular junction (NMJ)



ChAT = choline acetyltransferase; CoA = coenzyme A. The neuromuscular junction consists of the motor nerve terminal, muscle endplate with folded postsynaptic membrane, and synaptic cleft in between. Acetylcholine (ACh) is synthesised in the motor nerve and stored in nerve terminal vesicles. When the terminal is depolarised, it results in calcium ( $Ca^{2+}$ ) influx<sup>9</sup> that then releases ACh into the synaptic cleft. ACh interacts with its receptors on the post-synaptic membrane, which results in an endplate potential (EPP). A sufficiently large EPP spreads across the muscle fiber, initiating muscle contraction. ACh is then hydrolysed to choline and acetate by acetylcholinesterase (AChE) located on the endplate membrane. The nerve terminal actively takes up choline for further synthesis of ACh.

Table 3: Investigations in myasthenia gravis

- 1) AChR antibody titre
- 2) Tensilon test
- 3) EMG: repetitive nerve stimulation
- 4) Single-fiber EMG for abnormal neuromuscular transmission
- 5) CT mediastinum for thymic hyperplasia and thymoma

### Tensilon (Edrophonium chloride) test

Weakness in MG improves after intravenous edrophonium chloride, a short-acting cholinesterase inhibitor (ChEI). This test is most reliable for patients

with ptosis or nasal speech.<sup>15</sup> However, false negative tests may be seen in patients with early disease, severe fluctuations in symptoms or muscle atrophy.<sup>15</sup> The test should be repeated after exercise or in the evening, if the diagnosis is still strongly suspected. False positive tests may occur in motor neurone disease (where there is abnormal neuromuscular transmission caused by rapid denervation), Guillain-Barre syndrome, botulism, Lambert-Eaton myasthenic syndrome, polymyositis, cranial nerve syndromes with brainstem involvement, tumours of the orbital or parasellar region and bilateral intracavernous carotid aneurysm.<sup>16</sup> The sensitivity of the test is about 90% in both generalised and ocular MG,<sup>15</sup> with a specificity of about 90%.<sup>16</sup>

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Typical clinical features, e.g. ptosis, extraocular movement, proximal limb power and forced vital capacity may be serially monitored, before and after intravenous injections of placebo (saline) or Tensilon in a double-blind manner. For instance, 2 mg is injected intravenously and the response monitored for 1 minute, followed by 3 mg and then 5 mg bolus, if there is no improvement. Rarely, some patients may be very sensitive to the drug where even small doses may cause serious side-effects such as bradycardia and asystole.<sup>15</sup> Hence, resuscitation equipment should be available in case of an extremely sensitive patient. In selected cases, a bolus intravenous dose of atropine (0.6 mg) may be given prior to the test. Other common side-effects of Tensilon are increased lacrimation, nausea, salivation and abdominal cramps.

### Acetylcholine receptor (AChR) antibody titre

Elevated serum titres of AChR antibodies are found in about 80-90% of patients with generalised MG,<sup>17,18</sup> and in about 60% of pure ocular MG patients.<sup>17</sup> In Chinese, these antibodies are present in about 70% of generalised MG patients and in 30% of ocular MG.<sup>3</sup> However, seronegative tests do not exclude MG. Conversely, seropositive tests are found in systemic lupus erythematosus, biliary cirrhosis, amyotrophic lateral sclerosis, rheumatoid arthritis on penicillamine,<sup>8</sup> haematological diseases, bone marrow transplantation, thymoma without MG, tardive dyskinesia, in relatives of MG patients, and in the elderly with other autoimmune antibodies.<sup>18</sup> Hence, presence of AChR antibodies per se is not diagnostic of MG.

The antibody titre is not associated with the severity of MG. However, during the course of the disease in an individual patient, there is a good correlation between antibody titre and clinical improvement following thymectomy in about 80% of patients.<sup>19</sup> A similar correlation is also found in response to plasmapheresis.<sup>20</sup> Most patients remain seropositive, even in those with complete remission.<sup>18</sup> Seronegative patients are more likely to have purely ocular symptoms and their clinical features do not differ from seropositive patients.<sup>21</sup> A lower frequency of thymic pathology has been reported for seronegative patients.<sup>22</sup>

### Electromyography (EMG)

A decrease in compound muscle action potential CMAP amplitude (>10%; i.e. significant decremental

response) to repetitive nerve stimuli stimulation indicates impaired neuromuscular transmission. The responses from surface EMG may be recorded over the abductor digiti minimus or from more proximal muscles such as the trapezius. However, subjects with either mild symptoms or pure ocular MG may show normal responses. The sensitivity of the test ranged from about 30 to 90% in generalised MG, and about 4 to 50% in ocular MG.<sup>16</sup> The specificity of the test is about 90% for generalised MG and is even higher for ocular MG. False positive responses are observed in motor neurone disease, myotonic dystrophy, Lambert-Eaton myasthenic syndrome and other myopathies. A conventional needle EMG should also be performed in some cases to exclude polymyositis and thyroid myopathy that may mimic or coexist with MG.

Single-fiber (SF) EMG is the most sensitive test of impaired neuromuscular transmission. SF-EMG recordings are made while the patient voluntarily activates the muscle being studied. When action potentials are simultaneously recorded from two muscle fibers from the same motor unit, the time interval between the two potentials varies among consecutive discharges. The "jitter" is quantified as the mean difference between consecutive interpotential intervals. When neuromuscular transmission is impaired, the "jitter" is increased. Normal "jitter" in a clinically weak muscle excludes abnormal neuromuscular transmission as the cause of weakness. Increased muscle "jitter" is found in almost all MG subjects but is also found in other motor unit disorders with defects in neuromuscular transmission, e.g. neuropathy and myopathy. Conventional needle EMG should be performed when there is increased "jitter" to exclude disorders such as polymyositis, Eaton-Lambert syndrome, periodic paralysis, Miller-Fisher syndrome, botulism, motor neurone disease or organophosphate poisoning.

Based on the age of onset, thymic abnormalities and other immune variables, generalised MG patients can be divided into three main groups:

- a) onset before 45 years (mainly female), usually associated with thymic hyperplasia
- b) onset after 45 years (slightly more males) usually associated with thymic atrophy
- c) patients with thymoma, usually with no clear age and sex bias.

## Update Article

According to severity of clinical features, MG can be classified into five subtypes (Table 4).

### Management

#### General principles

The treatment should aim to relieve symptoms and achieve remission, to enable patients to return to their normal activities. Treatment is divided into symptomatic and immunomodulating therapies. (Table 5). The treatment should be tailored to the individual patient.

ChEI are used for symptomatic control. If significant or disabling symptoms persist despite optimal ChEI therapy, corticosteroids should be considered when there is no significant improvement six months to one year postthymectomy. Long-term azathioprine is indicated if they respond poorly to corticosteroids, or when high maintenance doses of corticosteroids are required. Plasmapheresis or pooled intravenous human IgG (IVIgG) provides rapid but short-term improvement for acute exacerbations. Thymectomy is indicated for long-term control for patients with thymic hyperplasia and is essential for patients with thymomas. The patients and their carers should be educated about MG, the need for regular assessments, and prompt medical attention when they deteriorate. Patients should carry a card listing contraindicated medications (Table 6).

#### Symptomatic treatment

##### Cholinesterase inhibitor

ChEI inhibits the hydrolysis of ACh by acetylcholinesterase at the synaptic cleft (Figure 1) such that ACh can stay in the synaptic cleft and interact with AChR for a longer duration. It may be the only drug that is required in some patients. The dose has to be titrated according to the response. The required dose may be increased with infections, stress or even menstruation. An optimal dose may be difficult to achieve in some patients where different muscle groups respond differently to the same dose of ChEI. We generally titrate the dosage to produce responses in muscles that cause the greatest symptomatic disability. Pyridostigmine is most often used because of its longer duration of action and may be commenced at 30 mg three times daily. The side-effects of ChEI are shown in Table 7.

### Immunomodulating treatment

#### Thymectomy

More than half the patients with thymic hyperplasia who underwent thymectomy had remission within two years.<sup>23</sup> Another 33% became asymptomatic on

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**Table 4: Subtypes of myasthenia gravis**

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- I. Pure ocular (ptosis, diplopia)
- II A. Mild generalised (ocular and extremities, no prominent bulbar signs)
- II B. Moderate generalised (ocular and/or bulbar signs, variable limb muscle involvement, and no crises)
- III. Acute fulminating generalised signs with prominent bulbar involvement and crises
- IV. Late severe generalised and prominent bulbar signs and crises

*(Osserman KE, Genkins G. Studies in myasthenia gravis: review of a twenty-year experience in over 1,200 patients. J Mount Sinai Hosp. 1971;38:497-537.*

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**Table 5: Modes of treatment for myasthenia gravis**

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- 1) General measures
  - 2) Symptomatic treatment
    - ChEI, physical aids and surgery for eye symptoms
  - 3) Immunotherapy
    - short-term: plasmapheresis, IVIgG
    - long-term: corticosteroids, azathioprine, other immunosuppressants, and thymectomy
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**Table 6: Drugs which are contraindicated or used with caution in myasthenia gravis**

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- 1) Aminoglycosides
- 2) D-penicillamine
- 3) Neuromuscular blockers (suxamethonium, alcuronium, vecuronium, atracurium)
- 4) Local anaesthetics (e.g. lignocaine)
- 5) Anti-arrhythmic (e.g. quinine, quinidine, procainamide)
- 6) Beta-blockers
- 7) Magnesium sulphate

*Note: High dose corticosteroids may initially worsen myasthenic symptoms*

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**Table 7: Side-effects of cholinesterase inhibitors**

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- 1) Dose-related muscarinic effects
    - gastrointestinal: nausea, vomiting, abdominal pain, and diarrhoea
    - respiratory: bronchoconstriction, pharyngeal and bronchial hypersecretion
    - ocular: miosis, pain, conjunctival congestion, ciliary spasm, glandular hypersecretion
  - 2) Massive overdose leads to impaired neuromuscular transmission, fatigability, increased weakness, fasciculations -cholinergic crisis
  - 3) Acute psychosis or bad dreams (bromism): rarely in patients who take high doses of pyridostigmine bromide
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pyridostigmine alone, and 11% were asymptomatic on corticosteroids. The extent of thymic hyperplasia is thought to correlate with the clinical response,<sup>23</sup> but other studies did not confirm this.<sup>24</sup> Seronegative MG may also improve with thymectomy.<sup>23</sup>

Thymectomy is indicated in all patients with thymoma and refractory symptoms, and in those less than 45 years old with generalised MG. Age per se is not a contraindication for thymectomy and individual cases of ocular MG patients may be considered. Control of MG following thymectomy on patients with thymoma is less clear. It may be impossible to resect some thymomas completely. The prognosis is more related to the extent of the tumour and is generally worse than those patients without thymoma.<sup>23,24</sup>

### Corticosteroids

Steroids are indicated when symptoms are not well controlled using ChEI. Pure ocular MG with disabling symptoms uncontrolled with ChEI may respond dramatically to low-dose steroids. At least 70% of MG patients respond clinically to steroids.<sup>25</sup> The improvement usually begins after two weeks of therapy. We prefer to use prednisolone instead of prednisone because the latter requires hepatic conversion to prednisolone. Prednisolone (60 to 80 mg daily) followed by lower dose alternate-day therapy of several years duration, produced remission of MG symptoms in about 30% of patients, and marked improvement in about 50% within 18 months of therapy.<sup>25</sup> Long-term improvement was obtained in 80% of patients. About 15% of the subjects were able to discontinue the

steroids. About 20% of those who achieved satisfactory response had exacerbations, which necessitated a return to higher doses or other forms of treatment.<sup>25</sup>

We suggest a gradual dose increment starting at 5 mg prednisolone daily with a weekly increase of 2.5 mg until symptoms improve. Its maximum dose is usually 60 to 80 mg daily. When improvement is achieved, the dose can be gradually reduced over months to the lowest dose (preferably less than 10 mg daily) necessary to maintain improvement. A dose reduction of more than 5 mg per month may provoke a relapse of symptoms.<sup>26</sup> Patients with bulbar weakness may be especially sensitive to exacerbations when steroids are initially given. Mild early exacerbation developed in about half of the patients initially treated with 60 to 80 mg daily oral prednisone, and severe exacerbations occurred in under 10% of patients.<sup>27</sup> Hence, the dose of steroids should be increased gradually.<sup>28</sup> Plasmapheresis or IVIgG may be used to provide short-term control over this period. Other immunosuppressants should be considered for patients who require more than 15 mg prednisolone daily. Steroid-induced hypokalaemia and myopathy can occasionally mimic MG symptoms. Various measures including calcium supplements may be taken to reduce long-term side-effects of steroids in women.

### Azathioprine

Azathioprine is converted in the liver to mercaptopurine, which possesses immunosuppressive and anti-inflammatory properties. Azathioprine is useful for its steroid-sparing effect, and should be considered in MG when the response to steroids is unsatisfactory, or the maintenance dose is greater than 15 mg prednisolone daily. It may also be used if there is unsatisfactory control with ChEI, or if steroids and/or thymectomy are contraindicated or not tolerated. Azathioprine used in combination with prednisolone is more efficacious compared to prednisolone alone. Adjunct azathioprine in seropositive MG reduces the maintenance dose of prednisolone and is associated with fewer treatment failures, longer remissions, and fewer steroid-induced side-effects.<sup>29</sup> We suggest starting azathioprine at 25 mg daily, with increments of 25 mg/week up to 100 mg/day or 3 mg/kg/day. Azathioprine has a slow onset of action, with a delay in therapeutic response of about six months. At least half the patients will relapse during dose reduction.<sup>30-32</sup> The incidence of serious side-effects of

azathioprine is low. Complete blood count and liver function tests should be monitored weekly during initiation of therapy and thereafter every three to six months. Side-effects of azathioprine include reversible marrow depression, opportunistic infections, and transient elevation of liver enzymes, acute idiosyncratic reaction and teratogenicity. Taking divided doses after meals will help to reduce gastrointestinal upset. Contraception is recommended during and for at least six months after cessation of therapy.

### **Other immunosuppressants – cyclosporine and cyclophosphamide**

Cyclosporine is a potent immunosuppressant, which may be considered in patients refractory to other forms of immunosuppressant therapy.<sup>33</sup> Plasma trough levels, blood pressure, renal function should be monitored regularly with doses adjusted accordingly. Its long-term use in MG is limited by nephrotoxicity. Cyclophosphamide is an alkylating agent that interferes with B-cell proliferation, hence suppresses antibody production. Significant potential side-effects and toxicity limit its use for refractory patients only.<sup>34</sup> Its side-effects include leukopenia, alopecia, dysuria, haemorrhagic cystitis, teratogenicity, sterility.

### **Plasma exchange (Plasmapheresis)**

Plasmapheresis removes circulating AChR antibodies. It acts rapidly<sup>35,36</sup> with improvement seen in more than 60% of acute MG cases.<sup>37,38</sup> It may be used for optimising control of MG prior to thymectomy, for post-operative deterioration, and as a short-term adjunct therapy to immunosuppressants in severely affected patients. Intermittent plasmapheresis may be considered for MG refractory patients who respond poorly to drugs or thymectomy. It involves the separation of plasma, which is then replaced with human albumin (5%) in saline supplemented with calcium and potassium. Typically, about 2 litres of plasma is exchanged per session, two or three times a week until there is improvement, which may occur within the first 24 hours. Often, the effects of plasmapheresis are only obvious after two days. The improvement may last for several weeks. There is no cumulative benefit from repeated courses of plasmapheresis.<sup>36</sup> The clinical response is correlated to a reduction in AChR antibody titre.<sup>20</sup> There is a significant haemodynamic shift during plasmapheresis

that may lead to hypotension, especially in septicaemia and haemodynamically unstable patients. Access to large veins may be a problem in some patients requiring central vein catheterization. Other potential side-effects include allergic reactions to human albumin, electrolyte disturbance, thrombophelitis, subacute bacterial endocarditis, pulmonary embolism and pneumothorax.

### **Intravenous immunoglobulin (IVIgG)**

It acts by reducing the production and increasing the clearance of autoantibodies.<sup>39</sup> It also inhibits the binding of activated complement to target T-cells,<sup>40</sup> thus suppressing complement-mediated motor end-plate destruction. Clinical response was seen in about 70% of patients,<sup>41,42</sup> and it serves an alternative therapy to plasmapheresis. IVIgG improves myasthenic symptoms within a few days of treatment. The improvement usually lasts up to 12 weeks.<sup>43</sup> A regime is 0.4 gm/kg body weight per day for five consecutive days may be considered. A randomized trial comparing the efficacy and tolerance between plasmapheresis (three exchanges) and IVIgG (0.4 gm/kg/Day for three or five days) did not show a significant difference in outcome.<sup>44</sup> Potential side-effects from IVIgG include transient flu-like symptoms with fever, chills, nausea, vomiting, headache and malaise in the first 24 hours. The headache and nausea may improve with slowing of the infusion. Other side-effects include transmission of viral hepatitis, anaphylactic reactions (especially in IgA deficiency), renal failure<sup>45</sup> and aseptic meningitis.<sup>46</sup>

### **Treatment in specific circumstances in myasthenia gravis**

#### **Ocular myasthenia gravis**

Ocular MG is generally associated with a less life-threatening disease, but 30 to 70% of patients who developed ocular symptoms at onset may develop generalised disease.<sup>5,47,48</sup> The risk of developing generalised disease is highest soon after onset. A diagnosis of ocular MG is usually made only if symptoms remain ocular after two years. About 45 to 70% of ocular MG patients are seropositive.<sup>17,49</sup> The pathogenesis, associated diseases and treatment strategy of ocular MG are similar to that of generalised MG. However, severe diplopia can be very disabling. Chronic ptosis and diplopia may benefit from simple appliances, spectacle modifications and prisms.

### MG associated with thymoma

MG patients with thymoma should have thymectomy.<sup>50</sup> For non-invasive thymomas, radical thymectomy is considered curative although follow-up CT thorax should be performed. Invasive thymomas should be considered for post-operative radiotherapy.

### Myasthenic crisis

MG crisis involves a rapid and severe deterioration of symptoms (within days), often with bulbar weakness and respiratory failure that require mechanical ventilation. It is a neurological emergency. The crisis often involves a mixture of myasthenic and cholinergic features, where the patient may take large doses of ChEI but the most affected muscles (usually the bulbar and respiratory) do not improve resulting in typical clinical features (Table 8). It is more common in patients with thymoma. The Tensilon test is unhelpful in distinguishing the different types of crises as different muscle groups respond differently. It is also risky as the patient may deteriorate further. The patient will require assisted ventilation and airway protection, and should be managed in an Intensive Care Unit. The conscious state, respiratory status including respiratory rate, forced vital capacity (FVC), continuous pulse oximetry and arterial blood gases, cardiovascular status and muscle strength should be monitored regularly. Anticipation and prompt respiratory support are vital as dysphagia, copious production of bronchial secretions and aspiration can

**Table 8: Clinical features of myasthenic crisis**

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- |   |  |
|---|--|
| 1) Cholinergic crisis   |  |
| – nicotinic overactivity (e.g. fasciculation, muscle cramps, muscle weakness)   |  |
| – muscarinic overactivity (e.g. abdominal cramps, diarrhoea, meiosis, profuse salivation, bronchial secretion, lacrimation) |  |
| 2) Myasthenic weakness  |  |
| – ptosis, diplopia  |  |
| – generalised limb and trunk weakness   |  |
| – respiratory muscle weakness with hypoventilation  |  |
| – facial and pharyngeal weakness resulting in dysphagia and dysarthria  |  |
| – facial diplegia, aspiration   |  |
| 3) Confusion due to hypercapnia and/or hypoxaemia   |  |
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rapidly develop and further exacerbate respiratory failure. Assisted ventilation is required if FVC is below 15 ml/kg-body weight or when the tidal volume drops to below 4 to 5 ml/kg body weights. ChEI may be stopped when the patient is ventilated, and restarted at lower doses, and readjusted according to the clinical response. Improvement may occur with just supportive measures, but it is expedited with plasmapheresis or IVIgG.<sup>43,51</sup> Appropriate investigations should be carried out to determine any precipitating factors, e.g. infection, aspiration pneumonia, surgery, initiation of high doses of steroids and over-rapid withdrawal of immunosuppressants. In about 30% of MG crisis, no precipitating factor is found.<sup>53</sup>

Mortality from myasthenic crisis has declined from over 40% in the early 1960s to about 5% in 1970s.<sup>52</sup> High pre-intubation serum bicarbonate level, small peak vital capacity, and age of above 50 years are predictors of prolonged intubation.<sup>53</sup> Poor functional outcome and mortality are related to co-existing medical conditions.<sup>53</sup>

### Anaesthetic management

Stress during operations and certain drugs (e.g. narcotics and sedatives) used perioperatively may exacerbate MG. Local and spinal anaesthesia are preferred over inhalational anaesthesia. Inhalational agents alone usually offer adequate muscle relaxation.<sup>54</sup> Depolarising neuromuscular blockers should be avoided if possible, as low doses may cause pronounced and long-lasting blockade. If neuromuscular blockers are necessary, a non-depolarising agent (e.g. alcuronium, vecuronium, atracurium) should be used at one tenth to half of the normal dose under careful monitoring.<sup>55</sup> These agents are eliminated rapidly, and hence can be titrated during surgery. A longer period of postoperative ventilatory support may be required even for patients with good pre-operative control of MG.

### Myasthenia gravis in pregnancy

The treatment of perinatal conditions, e.g. preeclampsia, preterm labour and infection may be altered in MG. The clinical course of MG in pregnancy is unpredictable even in individuals with stable disease. About 1/3 of patients improve, 1/3 deteriorate and the remaining 1/3 remain stable. Exacerbations in MG may

*(Continued on page 19)*



**Key messages**

1. Myasthenia gravis (MG) is an autoimmune disease associated with autoantibody-mediated destruction of nicotinic acetylcholine receptors in skeletal muscles and impaired neuromuscular transmission.
2. Consider the diagnosis of MG in patients with ptosis and diplopia, dysarthria, dysphagia and limb weakness, typically proximal.
3. Fluctuating symptoms and muscle fatigability are important clues to the diagnosis.
4. Associated autoimmune diseases, thymic hyperplasia and thymoma should be considered and screened for.
5. The management should aim at symptom-free remission or mild symptoms with satisfactory quality of life.
6. Acute exacerbation in MG, especially those involving respiratory distress and bulbar weakness, must be referred for intensive care, and may require intubation and ventilatory support.

occur in all three trimesters. The clinical course of one pregnancy does not predict that of subsequent pregnancies. Therapeutic abortions do not help to control MG in first-trimester exacerbations.<sup>56,57</sup>

Counselling should be carried out prior to conception. Steroids and other immunosuppressants may be discontinued or stopped. Cytotoxic agents are contraindicated during pregnancy due to potential teratogenicity but steroids may be continued. Exacerbations are more frequent for patients without thymectomy prior to pregnancy. The prevalence of neonatal MG is not affected by thymectomy.<sup>58</sup> However, thymectomy is rarely performed during pregnancy, as the long-term outcome of MG is not affected by a delayed operation. Plasmapheresis and IVIgG may be considered in exacerbations or MG crisis during pregnancy. The uterus consists of smooth muscle. Its contractions are not mediated by nicotinic ACh receptors and hence are unaffected in MG. However, the voluntary expulsion of the fetus involves skeletal muscles during the second stage of labour and this may be compromised in MG. Regional anaesthesia and pudendal block may be performed for pain relief and caesarean section. Medications that potentiate myasthenic weakness should be avoided if possible. Magnesium sulphate may exacerbate MG symptoms and is contraindicated for pre-eclampsia.<sup>59</sup>

Transient MG affects 10 to 20% of neonates.<sup>2</sup> Affected newborns feed poorly during the first three days and present with a feeble cry, inadequate sucking, generalised muscle weakness, and respiratory distress.<sup>2</sup> Symptoms last for an average period of three weeks although it may continue for up to 12 weeks. Close observation, supportive measures, and ChEI may be required. The risk of neonatal MG is unrelated to maternal MG status or AChR antibody titres.<sup>60</sup> Myasthenic mothers may breast-feed the baby. In severe postpartum exacerbations, maternal AChR antibodies may pass to the infant through breast milk, and hence may exacerbate neonatal MG. It may be reasonable to avoid breast-feeding if symptoms of neonatal MG develop. Muscarinic symptoms have been described in infants of mothers taking ChEI.<sup>61</sup>

**Role of family practitioners in the treatment of MG**

Many patients with MG present with typical clinical features but some cases may be easily misdiagnosed. The diagnosis should always be considered in any patient presenting with diplopia, ptosis, and bulbar or proximal muscle weakness. Diurnal variations in the symptoms should raise a high index of suspicion. A definitive diagnosis should be established as early as possible. Patients with suspected MG presenting with acute respiratory distress and bulbar dysfunction should be referred to neurological units urgently. The co-existence of other autoimmune diseases should always be considered in any MG patient, even in those who have had the disease for a long time. Patients, especially with generalised symptoms, must be screened for thymic hyperplasia and thymoma. Some MG patients may be *refractory to treatment and should be referred for further management by a neurologist.* ■

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