Update on myasthenia gravis

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Myasthenia gravis is an autoimmune disorder caused by autoantibodies against the nicotinic acetylcholine receptor on the postsynaptic membrane at the neuromuscular junction and characterised by weakness and fatigability of the voluntary muscles. It has a bimodal peak of incidence with first peak in the third decade and the second peak in the sixth decade. It is probably underdiagnosed in the very old population. Our understanding of the pathogenesis, immunology, and molecular biology of myasthenia gravis has greatly improved in last three decades. It is almost always possible to establish the diagnosis of myasthenia gravis with the current tests. The modern treatment is highly successful and the mortality of treated myasthenia gravis is practically zero. However, there are still important gaps in our knowledge of the origin of myasthenia gravis, the factors that contribute to chronic disease, and the way to cure the disease. In this article the current knowledge of the various aspects of myasthenia gravis are outlined.

Myasthenia gravis is a potentially serious but treatable organ specific autoimmune disorder characterised by weakness and fatigability of the voluntary muscles that is caused by autoantibodies against the nicotinic acetylcholine receptor (AChR) on the postsynaptic membrane at the neuromuscular junction.1,2 Thomas Willis (1672) was probably the first to describe patients with weakness of limb muscles increasing during the course of the day and progressive tongue weakness provoked by "long, hasty or laborious speaking".3 It was more than two centuries later when another patient with bulbar and limb muscle weakness who died of respiratory failure was reported.4 The lesion was initially thought to be in the medulla oblongata but necropsy did not show any abnormality in the medulla. Subsequently, several case reports describing patients with the early or predominant bulbar weakness, and those with the weakness worsening during the course of the day appeared in the literature. Jolly (1895) described a progressive decline in the tetanic tension of the indirectly stimulated muscles with the repeated stimulations that improved with rest. He gave the disease its name: myasthenia gravis pseudoparalytica.5 The earlier reports suggested a "toxin probably of microbial origin" or "some toxic, probably autotoxic, agent" causing damage of the lower motor neurons to produce myasthenic weakness. The demonstration by Dale and Feldberg of acetylcholine as a neurotransmitter at the motor endplate paved the way for the future developments in pathogenesis, diagnosis, and the treatment of myasthenia gravis.6 Harvey and Marsland described the decremental response of the evoked muscles to repeated stimuli in myasthenia gravis.7 Simpson proposed a new theory that myasthenia gravis was an autoimmune disorder based on its association with the other autoimmune diseases, the thymic abnormalities noted in myasthenia gravis, and the fluctuating course of the disease.8 That the damage in myasthenia gravis is at the postsynaptic level was demonstrated by Engel and Santa in ultrastructural studies of the motor endplate.9 Neostigmine, an orally administered anticholinesterase, was first used in myasthenia gravis in 1935.10 Subsequently, corticosteroids11 and other immunosuppressants12 were found to be useful in treatment and Blalock reported beneficial effects of thymectomy.13 Lindstorm and his team demonstrated circulating antibodies directed against the AChR protein in up to 87% of cases of myasthenia gravis.14 Recently, antibodies that bind to MuSK, a muscle specific protein kinase, have been described in a subgroup of patients with myasthenia gravis who do not have antibodies against AChRs.15

Muscular weakness and fatigability are the hallmarks of myasthenia gravis. They are caused by an antibody-mediated autoimmune attack directed against AChRs at neuromuscular junctions. There are several mechanisms by which the autoantibodies reduce the number of available AChRs at neuromuscular junctions. The molecular structure of nicotinic AChR is now well characterised and the receptor has been purified from a variety of sources, including human muscle. An experimental model of myasthenia gravis has been produced by immunisation of animals with AChRs. This has greatly helped our understanding of the disease mechanisms. There have been significant advances in the diagnosis and treatment of myasthenia gravis. It used to be a very disabling and often fatal (and, hence, the name gravis) disease in the past. However, modern immunotherapy has dramatically improved the prognosis and nearly all patients are now able to lead full, productive lives.

Despite these advances, there are still important gaps in our knowledge. We do not know the factors that initiate and maintain the autoimmune response in myasthenia gravis. A

Abbreviations: AChR, acetylcholine receptor; EPP, endplate potential; MRI, magnetic resonance imaging; MuSK, muscle specific protein kinase
large amount of work is in progress to elucidate these mechanisms.

EPIDEMIOLOGY

Myasthenia gravis is the commonest disorder affecting the neuromuscular junction. Its prevalence has been reported as 2–7/10 000 population in the UK14 and around 1.5/10 000 in central and western Virginia.15 In a very large population based study of the epidemiology of myasthenia gravis in Greece,6 the average annual incidence was found to be 7.40/ million population/year (women 7.14; men 7.66), and the point prevalence rate was 70.63/million (women 81.58; men 59.39). Myasthenia gravis can present at any age, but there is a bimodal peak of incidence, with the first peak in the third decade (predominantly affecting women) and the second peak in the sixth and seventh decades (predominantly affecting men). It has been suggested that incidence falls after 70 years of age. However, in a recent population based UK study using AChR antibody as a diagnostic tool, it was shown that myasthenia gravis was substantially under-diagnosed in people >75 years.21

CLASSIFICATIONS OF MYASTHENIA GRAVIS

Myasthenia gravis can be classified according to the age of onset, presence or absence of anti-AChR antibodies, severity, and the aetiology of the disease.

Age of onset

Myasthenia gravis can be classified as transient neonatal or adult autoimmune. Transient neonatal myasthenia gravis is due to transfer of maternal anti-AChR antibodies through the placenta to the newborn reacting with the AChR of the neonate. Only 10%–15% of the infants with these antibodies manifest symptoms of myasthenia gravis (hypotonia, weak cry, respiratory difficulty, etc) within the first few hours of life. Symptoms usually resolve spontaneously within 1–3 weeks, though temporary supportive treatment and pyridostigmine may be required.

Presence or absence of anti-AChR antibodies

Myasthenia gravis can be classified as seropositive or seronegative.

Seropositive

This the commonest type of acquired autoimmune myasthenia gravis. Nearly 85% of patients with generalised myasthenia and 50%–60% with ocular myasthenia gravis test positive for anti-AChR antibodies by radioimmunoassay. This entity is the most studied form of myasthenia gravis.

Seronegative

About 10%–20% of patients with acquired myasthenia gravis do not have anti-AChR antibodies detectable by radioimmunoassay. Recently, antibodies that bind to MuSK have been reported in a subgroup of these patients.7 It is proposed that the presence of antibodies against MuSK appears to define a subgroup of patients with seronegative myasthenia gravis who have predominantly localised, in many cases bulbar, muscle weaknesses, reduced response to conventional immunosuppressive treatments, and muscle wasting.8

Essentially, seronegative myasthenia gravis is likely to be an autoimmune disorder involving antibodies against one or more components of the neuromuscular junction that are not detected by the current anti-AChR radioimmunoassay. In addition to anti-MuSK antibodies, plasma from patients with myasthenia gravis contains other distinct humoral factors: IgG antibodies that reversibly inhibit AChR function and a non-IgG (possibly IgM) factor that indirectly inhibits AChR function.

Severity

Osserman’s original classification divides adult myasthenia gravis into four groups based on the severity of the disease:23

1. Ocular myasthenia, where disease is confined to ocular muscles.
2. Generalised myasthenia gravis of mild (a) or moderate (b) intensity.
3. Severe generalised.

Recently, this classification has been modified by an ad hoc committee of the American myasthenia gravis foundation24 to standardise it for research purposes into following types:

(I) Any ocular weakness; may have weakness of eye closure; strength of all other muscles being normal.

(II) Mild weakness other than ocular muscles, +/- weakness of ocular muscles of any severity. Ila: predominant limb and/or axial involvement; Iib: predominantly oropharyngeal and/or respiratory involvement.

(III) Moderate weakness affecting muscles other than ocular muscles, may have ocular weakness. Ila: predominant limb and/or axial involvement; Iib: predominantly oropharyngeal and/or respiratory involvement.

(IV) Severe weakness affecting muscles other than ocular muscles, may have ocular weakness. Iva: predominant limb and/or axial involvement; IVb: predominantly oropharyngeal and/or respiratory involvement.

(V) Defined by intubation with or without mechanical ventilation, except when employed during routine postoperative management. The use of feeding tube without intubation places the patient in class IVb.

Aetiology

There are four classes based on the aetiology:

1. Acquired autoimmune.
2. Transient neonatal caused by the passive transfer of maternal anti-AChR antibodies
3. Drug induced: D-penicillamine is the prototype of drug induced myasthenia gravis. Clinical presentation may be identical to typical acquired autoimmune myasthenia gravis and the antibody to AChR may be found.25 Disease tends to remit after cessation of the drug. Other drugs that can cause myasthenia-like weakness or that exacerbate weakness of myasthenia gravis include curare, aminoglycosides, quinine, procainamide, and calcium channel blockers.
4. Congenital myasthenic syndromes (AChR deficiency, slow channel syndrome, and fast channel syndrome) are distinct heritable disorders of postsynaptic neuromuscular transmission with characteristic age of onset, pathology, electrophysiology, and treatment.

AETIOPATHOGENESIS OF MYASTHENIA GRAVIS

It is important to understand the basic concepts of anatomy and physiology of the neuromuscular junction to comprehend the aetiopathogenesis of myasthenia gravis and related disorders (fig 1).

Anatomy of a normal neuromuscular junction

The synaptic junction involving a motor nerve terminal and the muscle membrane is the most extensively studied
Acetylcholine is synthesised in the nerve terminal from acetyl CoA and choline by the enzymatic action of choline transferase. It is packaged in the vesicles and is released into the synaptic cleft on arrival of a nerve impulse. Each vesicle contains from nearly 8000 to 13 000 acetylcholine molecules, termed the “quanta”. Release of the acetylcholine into synaptic cleft by nerve stimulus requires calcium and the process is called stimulus-secretion coupling. Calcium influx occurs through the voltage gated calcium channels that are situated near the release sites. In Lambert-Eaton myasthenic syndrome, autoantibodies against these voltage gated channels produce muscle weakness by interfering with the acetylcholine release. The entry of calcium triggers the fusion of the vesicle with the presynaptic nerve cell membrane. Subsequently, the contents of the vesicles are released into the synaptic cleft by the process of exocytosis. A number of proteins are involved in this process. Destruction of any of these proteins (for example, by various serotypes of botulinum toxin) can interfere with the quantal release of acetylcholine to cause paralysis. Once acetylcholine is released, the presynaptic membrane is recaptured by pinocytosis, and the vesicles are remade and repleted with acetylcholine. It is worth noting that the acetylcholine release sites are located opposite to the peaks of the folds in the postsynaptic membrane where AChRs are clustered at high concentrations.

Synaptic clefts
Synaptic clefts are divided into primary and secondary synaptic clefts. The primary cleft is the space that separates presynaptic nerve membrane from the postsynaptic membrane muscle membrane. It is approximately 70 nm wide and its length is equal to the presynaptic membrane. It has no lateral boundaries and, therefore, it communicates with the extracellular space. Acetylcholine is released into this space before it acts on the AChR. The secondary clefts are the spaces between the junctional folds of the postsynaptic membrane and they communicate with the primary cleft. Acetylcholinesterase is most highly concentrated in the secondary clefts. It hydrolyses acetylcholine to terminate neuromuscular transmission so that muscle fibre can be stimulated again. The acetylcholinesterase inhibitors are used in the treatment of myasthenia gravis. By inhibiting acetylcholinesterase, they increase the availability of acetylcholine to react with the AChR and, therefore, improve transmission at the neuromuscular junction. However, an excess of acetylcholine can desensitise receptors and may worsen the weakness, the so-called cholinergic crisis. Acetylcholinesterase can be irreversibly blocked by the organophosphorous compounds. The genetic defects leading to acetylcholinesterase deficiency at the motor endplate may produce muscle weakness manifesting in infancy or childhood.

Postsynaptic
The surface of a muscle cell membrane opposite to the nerve cell terminal at the neuromuscular junction is thrown into folds (junctional folds). The normal junctional fold has a slender stalk and a terminal expansion (“peak”). AChRs are mostly concentrated in the peaks of these folds. Acetylcholinesterases are primarily located in the secondary clefts and they hydrolyse acetylcholine as described above. The structure, function, and the molecular biology of the AChR are now well understood. This has led to a better understanding of myasthenia gravis, congenital myasthenic syndromes, and the effects of several drugs and toxins that work through the neuromuscular junction.

The AChR is a glycoprotein comprising five subunits arranged around a central channel (fig 2). In an innervated muscle, these subunits are two α subunits, one β subunit, one δ subunit, and one ε subunit. In an immature or denervated muscle, the ε subunit is replaced by a γ subunit. In the resting state, ion channel of the AChR is closed. When both the α subunit binding sites are occupied, the AChR molecule twists slightly like a Chinese purse, opening the channel and allowing the entry of sodium ions into the interior of the muscle cell, which results in partial depolarisation of the postsynaptic membrane and generation of an excitatory postsynaptic potential. If the number of open sodium channels reaches threshold, a self propagating muscle action potential is generated in the postsynaptic membrane. Some of the congenital myasthenic syndromes (for example, slow channel syndrome and fast channel syndrome) are caused by the abnormalities of the AChR channels. Genes for all the subunits of the AChR have been cloned, and it is possible to produce these subunits by genetic engineering.
As mentioned above, AChRs are mostly concentrated in the peaks of these folds. This clustering of AChRs involves an interaction of several proteins including a MuSK—the protein now found to be a target for antibodies in seronegative myasthenia gravis. There is a constant turnover and renewal of the AChRs at the neuromuscular junction allowing a near complete recovery in myasthenia gravis after the autoimmune attack is brought under control.

Physiology of a normal neuromuscular junction

Acetylcholine is released from the presynaptic membrane either spontaneously or as a result of the nerve impulse. Released acetylcholine binds to the AChR. As explained above, the receptor’s cation channel opens transiently, producing a localised electrical endplate potential. If the amplitude of this potential is sufficient, it generates an action potential that spreads along the length of the muscle fibre, triggering the release of calcium from internal stores and leading to muscle contraction. Spontaneous release of acetylcholine involves contents from a single vesicle, giving rise to a low amplitude depolarisation of the muscle membrane, leading to muscle contraction. During repeated nerve stimulations, the amount of acetylcholine released progressively decreases after the initial few stimuli, the so-called “synaptic rundown”. Under normal conditions, the amplitude of the EPP is more than necessary to produce an action potential triggering muscle contraction. This excess is termed “safety factor”. Safety factor depends on several factors including the amount of acetylcholine released and the number and integrity of the AChRs, among others.29 In myasthenia gravis, this safety factor is reduced. The reduced safety factor in association with a normal “synaptic rundown” leads to progressive decline in muscle power on repeated stimulations in myasthenia gravis.

Anatomy and physiology of the neuromuscular junction in myasthenia gravis

The major abnormalities of the neuromuscular junction in myasthenia gravis include (a) reduced number of the AChRs leading to reduced length of the postsynaptic membrane, (b) shortening of the synaptic folds due to destruction of the terminal expansions, and (c) widening of the synaptic clefts caused by the shortening of the junctional folds (fig 3). These changes are brought about by autoimmune attack on the postsynaptic membrane. It is worth noting that the abnormalities in myasthenia gravis are postsynaptic in location (in contrast to presynaptic abnormality in Lambert-Eaton syndrome). The consequence of these abnormalities is a reduced safety factor. As previously discussed, reduction in safety factor coupled with a normal “synaptic rundown” leads to progressive reduction in amplitude of the EPP. This leads to myasthenic weakness characterised by fatigue on exertion.

IMMUNE PATHOGENESIS OF MYASTHENIA GRAVIS

Role of AChR antibodies

It is now well established that myasthenia gravis is an antibody-mediated disorder of the neuromuscular junction. There are several lines of evidence supporting the role of antibodies in the pathogenesis of myasthenia gravis: (A) AChR antibodies are found in nearly 80%–90% of patients with generalised disease. (B) Circulating anti-AChR antibodies are found in cases of transient neonatal myasthenia gravis and the titre of the antibody declines as the patient recovers. (C) Passive transfer of IgG from myasthenic patients to experimental mice produces disease similar to myasthenia. (D) Plasmapheresis lowers the levels of AChR resulting in the improvement in myasthenia. (E) Antibody binds to AChRs at the neuromuscular junction. (F) An experimental model of myasthenia gravis can be produced by immunisation of various animals with purified AChR. Antibody response in myasthenia gravis is polyclonal. In an individual patient, antibodies are composed of different subclasses of IgG. In most instances, antibody is directed against the main immunogenic region on the α subunit. The α subunit is also the site of acetylcholine binding, though the binding site for acetylcholine is not the same as the main immunogenic region. Details of the mechanisms of humoral pathogenesis of myasthenia gravis are beyond the scope of this article and readers are advised to refer to an excellent article on this topic.30 In summary, destruction of the AChRs by the antibody is brought about by following mechanisms:

(A) Antibodies cross linking with the AChR with subsequent accelerated endocytosis and degradation of the AChRs by muscle cells; (B) antibody blocking the binding sites of the AChRs; and (C) complement-mediated destruction of junctional folds of the postsynaptic membrane. There is evidence for each of the mechanisms. The serum concentration of AChR antibodies in different patients does not correlate with the clinical severity of myasthenia gravis. This finding suggested that the antibodies might vary in their capacity to produce myasthenic weakness. It has been suggested that the severity of weakness in myasthenia gravis depends on the functional activities of the antibodies (in accelerating degradation or blocking AChRs, their ability to bind complement, etc) and the differences in neuromuscular junctions in different patients, or even in different muscles of an individual patient.

Seronegative myasthenia gravis

As discussed above, about 10%–20% of patients with myasthenia gravis do not have anti-AChR antibodies and are called seronegative. It has been shown that these patients have circulating antibodies that are not detectable by the radioimmunoassay for AChR antibodies. These antibodies are capable of destroying AChRs in culture systems and when transfused to mice, can produce an illness similar to myasthenia gravis. Recently, Hoch et al have shown that at least some of these seronegative patients have antibodies in their sera that bind to MuSK.31 As previously described, MuSK is one of the proteins involved in anchoring and
clustering of AChRs at the postsynaptic membrane. It is no surprise that interfering with these processes by antibodies can impair transmission at the neuromuscular junction. The antibodies that target other components of the neuromuscular junction but are not detectable by the currently available tests may be responsible for the remaining cases of myasthenia gravis.

Role of T-cells

Though myasthenia gravis is predominantly caused by the antibodies (produced by B-cells) against AChRs, T-cells have also been shown to be important in the pathogenesis of the disease. T-cells from patients with myasthenia gravis respond to stimulation with AChRs. In vitro, T-cells can augment production of the antibody against AChR. Peripheral blood lymphocytes of patients include T-cells and B-cells specific for AChRs. The helper T-cells (CD4+) respond to antigen that has been enzymatically degraded, or processed, by antigen-presenting cells and is associated with the major histocompatibility complex class II molecules. The activated T-cells help AChR specific B-cells. It is proposed that the T-cells produce the help to the B-cells by means of surface molecules and cytokines, resulting in B-cell proliferation and the secretion of AChR specific antibody. Future studies should shed more light on the exact role of the T-cells in the pathogenesis of myasthenia gravis. It is still not known how the tolerance to AChR (and other components of the neuromuscular junction) is broken to initiate the immune response. The role of the thymus is considered to be important in this context.

Role of thymus

The association of myasthenia gravis and thymoma was noted more than 200 years ago. Thymic abnormalities are found in nearly 75% of patients with myasthenia gravis. Of these, germinai hyperplasia is noted in 85% and thymic tumours in 15%. Antistriated muscle antibodies are found in 90% of patients with myasthenia gravis and a thymoma. Muscle cell-like cells (myoid cells) are found in thymus that express surface AChRs. These cells are surrounded by the helper T-cells and the antibody-presenting cells. It is theorised that these myoid cells are the source of autoantigen, AChR. Any alteration (for example, by viruses or genetic factors) may break down the tolerance and lead to autoimmunity but, so far, there is no evidence to support this. The other hypothesis suggests that myasthenia gravis may be triggered by a molecular mimicry—that is, an immune response to an infectious agent that resembles the AChR.

CLINICAL FEATURES OF MYASTHENIA GRAVIS

Typically, patients present with a history of weakness and fatigability of muscles on sustained or repeated activity that improves after rest. The symptoms vary from day to day and from hour to hour, typically increasing toward evening. The factors known to increase weakness include exertion, hot temperatures, infections, emotional upsets, certain drugs (for example, aminoglycosides, phenytoin, local anaesthetics, surgery, menses, and pregnancy (table 1). The most commonly affected muscles in the decreasing order of frequency are: levator palpebrae superioris, extraocular muscles, proximal limb muscles, muscles of facial expression, and neck extensors. The external ocular muscles are affected initially in about 50% and eventually in 90% of cases. Ptosis (weakness of levator palpebrae) that is often partial and may be unilateral, is a common presenting feature. It is often fluctuating in nature.

The presence of an eyelid twitch response (Cogan’s lid twitch) is characteristic of myasthenia gravis. When the patient’s eyes are directed downward for 10–20 seconds and the patient is then instructed to make a vertical saccade back to primary position, the upper eyelid elevates and either slowly begins to droop or twitches several times before settling into a stable position. This phenomenon is caused by the rapid recovery and easy fatigability of myasthenia gravis. This test is not pathognomonic of myasthenia gravis as it can occur with the brain stem or ocular disorders. The ptosis improves after a period of sleep (the so-called “sleep test”) or with application of the ice on the lid (the so-called “ice test”).

There may also be a weakness of orbicularis oculi leading to difficulty in eye closure. The ocular palsies are often asymmetric and fluctuating, and can mimic various types of ophthalmoplegias, including internuclear ophthalmoplegia, ocular motor nerve palsies, or gaze palsies. Saccades are typically hypometric that begin with normal velocity but eventually show a decrease in velocity (intrarasaccadic fatigue) and undershoot the target. The pupils are typically spared in the myasthenia gravis.

The face may appear expressionless. The mouth may be open and patient may have to support his/her jaw with a finger. When the patient attempts to smile, the face may take an appearance of a “snarl”. This is due to the fact that the corners of the mouth are not drawn up and out while the levators expose the canines. Nasal character of the voice and nasal regurgitation may result from palatal weakness. Dysphonia may result from laryngeal weakness. Dysphagia is a common presentation due to the fatigue of muscles involved in chewing and swallowing. The voice becomes progressively softer during conversation. The weakness may remain confined to ocular muscles in about 10% of patients (ocular myasthenia), but in most cases it progresses to involve other facial and limb muscles (generalised myasthenia).

The progression of weakness in myasthenia gravis usually occurs in a craniocaudal direction (as in Eaton-Lambert syndrome): ocular→facial→lower bulbar→truncal→limb muscles. The weakness of intercostal muscles and diaphragm leads to dyspnoea on exertion or at rest. The orthopnoea with rapid resolution on sitting up and diaphragmatic paradox are important clinical signs of neuromuscular breathlessness. Breathlessness can develop suddenly over hours and these patients should be closely monitored with regular measurements of their forced vital capacity.

In severe cases (class V of modified Osserman’s grading), patients may require intubation and mechanical ventilation. With the limb muscle involvement, fatigue on exertion becomes obvious to the patients. The deep tendon reflexes are normal or brisk and there are no objective sensory signs. Weakness may fluctuate from day to day or over long periods of time, making objective assessment difficult in some cases. Moreover, spontaneous remissions of variable periods are known particularly in the early stages, though complete remissions are rare. Characteristic clinical features are summarised in box 1.

OTHER ASSOCIATED DISEASES

The association of the thymic abnormalities, including thymic hyperplasia and thymomas with myasthenia gravis has already been mentioned. Thymic tumours can be readily

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<tr>
<th>Factors that increase the weakness in myasthenia gravis</th>
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<tr>
<td>Physical exertion</td>
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<td>Hot temperature</td>
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<td>Emotional upsets</td>
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<tr>
<td>Infections</td>
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<td>Hyperthyroidism</td>
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<td>Hypokalaemia</td>
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Table 1
Box 1: Characteristic clinical features of myasthenia gravis

- Can present at any age, typically bimodal peak, with first peak in the third decade and the second peak in sixth and seventh decades (‘young women and old men’).
- Weakness and fatigue of the voluntary muscles are the most important features. Symptoms worsen or appear on exertion and improve at rest or by anticholinesterases. Typically, there is a diurnal variation, with worsening of symptoms in the later part of the day.
- Ocular muscle weakness is usually the initial presentation and may be the only feature through the course in about 10% of patients. The ptosis (and diplopia) is exacerbated by the prolonged upward gaze toward a fixed target for one minute.
- In most cases, weakness progresses from ocular muscles to involve other muscles in a craniocaudal direction. The weakness of intercostal muscles and diaphragm leads to dyspnoea on exertion or at rest. The orthopnoea with rapid resolution on sitting up and diaphragmatic paradox are important clinical signs of neuromuscular breathlessness.
- Deep tendon reflexes are intact or may be brisk.
- There are no objective sensory deficits.
- In severe cases, respiratory failure may ensue, needing intubation and mechanical ventilation.
- Symptoms may fluctuate and there may be remissions of variable periods, particularly at early stages.

Diagnosed on computed tomography or magnetic resonance imaging (MRI). The thymus can be normally visualised up to the mid-30s. However, if a thymus is still visualised in a patient >40 years or at any time if the size of thymus increases, the possibility of a thymoma should be entertained. Thyroid disorders (hyperthyroidism, hypothyroidism, or a goitre) are seen in nearly 13% of cases. Hyperthyroidism may worsen myasthenia gravis. The other autoimmune diseases that are known to be associated with myasthenia gravis include rheumatoid arthritis, pernicious anaemia, systemic lupus erythematosus, sarcoidosis, Sjögren’s disease, polymyositis, ulcerative colitis, and pemphigus. It is important to routinely screen for these autoimmune disorders in patients with myasthenia gravis. The increased incidence of non-thymic malignancies has also been reported in patients who have had not undergone thymectomy, with the incidence returning to the expected normal level after thymectomy.

**DIAGNOSIS OF MYASTHENIA GRAVIS**

In patients with a characteristic history it may be easy to make a diagnosis on clinical grounds alone. However, it is important to confirm diagnosis of myasthenia gravis before committing patients to long term treatment. The tests often used to diagnose myasthenia gravis are summarised in the table 2. It should be emphasised that the diagnosis of myasthenia gravis is mostly based on the results of the test for the antibody against AChR and the neurophysiological tests. The Tensilon test should only be used where the diagnosis is required urgently and the facilities for full resuscitation are available.

**(A) Edrophonium (Tensilon) test**

Edrophonium is an AChE inhibitor that works within a few seconds (30 seconds) and the effect lasts for a few minutes (about five minutes). It is administered intravenously. It is desirable to use a placebo injection (for example, normal saline) before the edrophonium injection. There should be a demonstrable weakness of the part (for example, ptosis or slurred speech) and an inability to sustain a posture (of the outstretched arm) to monitor the response. A fractionated dose is usually employed where initially 1–2 mg of the drug is administered and remaining 8–9 mg is given only if there is no response until 60 seconds after the first dose. The edrophonium test is associated with a low, but serious risk of bradycardia and/or hypotension. Therefore, this test should only be carried out where diagnosis of myasthenia gravis is required urgently and there are facilities for full resuscitation. The test is reported as positive if there is a definitive improvement in weakness. This suggests a diagnosis of myasthenia gravis. However, the test can be positive in other conditions, for example, amyotrophic lateral sclerosis, polymyelitis, peripheral neuropathies, brain stem lesions, ocu-lomotor denervation, chronic external ophtalmoplegia, mitochondrial myopathies, and even in normal persons.

**(B) Ice pack test**

This test can be employed when ptosis is present. The application of an ice pack to lids of the affected eyes improves ptosis due to myasthenia gravis in 80% of cases but it did not improve in ptosis due to other aetiologies. Response is explained on the basis of improvement in safety factor of the neuromuscular junction with local cooling presumably caused by slowing the kinetics of AChRs. The response is not entirely caused by rest. This test is much simpler than the edrophonium test and does not require cardiac monitoring. However, this test is rarely performed in UK.

Table 2: Summary of the tests used in diagnosis of myasthenia gravis

<table>
<thead>
<tr>
<th>Test</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Edrophonium (Tensilon test)</td>
<td>Easy to administer, no need for expensive equipment. Limitations: false positives and false negatives, occasional serious side effects, for example, hypotension and arrhythmias.</td>
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<tr>
<td>Ice test</td>
<td>Nearly 80% sensitive and highly specific to diagnose myasthenic ptosis, no need for cardiac monitoring, can be done in an office setting. Not commonly used, applicable only when ptosis is present.</td>
</tr>
<tr>
<td>AChR antibody in serum</td>
<td>Nearly 80%–85% sensitive in generalised and 60%–70% in ocular myasthenia gravis, highly specific, non-invasive, now widely available. May be the diagnostic “gold standard”. Titrations do not always correspond with the severity of myasthenia gravis.</td>
</tr>
<tr>
<td>Repetitive nerve stimulation</td>
<td>Sensitivity around 75%. Uncomfortable to patient, not specific. Not reliable if the limb is cold, or patient on acetylcholinesterase inhibitors.</td>
</tr>
<tr>
<td>Single fibre electromyography</td>
<td>Most sensitive test. Needs costly equipment, not specific.</td>
</tr>
<tr>
<td>Anti-MuSK antibodies</td>
<td>Found in a subset of seronegative myasthenia gravis.</td>
</tr>
<tr>
<td>Computed tomography/MRI of chest</td>
<td>To diagnose associated thymic tumours. Non-invasive. Greater yield in patients &gt;40 years of age. May be used post-thymectomy to look for residual thymic tissue in patients who deteriorate unexpectedly.</td>
</tr>
<tr>
<td>MRI brain</td>
<td>In cases where a structural brain stem lesion is possible.</td>
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</table>
(C) Anti-AChR antibody test
Vincent and Newsom-Davis developed a radioimmunoassay test to detect the antibodies that bind to AChRs.17 The development of this test has remarkably changed the diagnostic evaluation of myasthenia gravis and is now considered a diagnostic “gold standard”. These antibodies are found in nearly 80%–85% of patients with generalised myasthenia gravis and 50%–60% cases of ocular myasthenia gravis. This test is highly specific for myasthenia gravis. In fact, because of its high specificity, this test has been used in large population based studies to determine the incidence and the prevalence of the disease.20,21 Antibody titres do not correlate with disease severity across the patient population—that is, mild disease can be associated with a high titre and a severe disease may be associated with a low titre. However, in an individual patient, the titre does correlate with the disease severity and a decrease in titre means favourable response to the treatment (for example, plasmapheresis). A strong correlation between a change in the anti-AChR concentration and a change in clinical condition was noted during treatment with prednisone or immunosuppression and in the period after thymectomy, whereas no changes in anti-AChR concentrations were found if improvement was caused by the effect of anticholinesterases or if deterioration was caused by infection or emotion.18

(D) Anti-MuSK antibodies
It is well known that about 10%–20% of patients do not have anti-AChR antibodies in their sera (seronegative myasthenia gravis). However, targets for antibody attack other than the AChR were not known until recently. It was a collaboration between Vincent et al in UK and a German scientist (Hoch) that led to the recognition of a new target for antibody attack in myasthenia gravis.19 This region in the neuromuscular junction is a protein called muscle specific protein kinase or MuSK. MuSK is very important during development of the nerve muscle junction, because it controls the concentration and number of AChRs on the junctional folds. The role of MuSK during adult life is not clear. This group found antibodies to MuSK in some of the patients with seronegative myasthenia gravis but not in sera from normal persons. Interestingly, MuSK antibodies were not found concurrently with anti-AChR antibodies.

(E) Electrophysiological tests
Electrophysiological tests include repetitive nerve stimulation test and single fibre electromyography. The repetitive nerve stimulation test shows progressive reduction in the amplitude of the compound muscle action potential from the first stimulation when a nerve is subjected to repetitive supramaximal electrical stimulations at a frequency of 3 Hz. In normal subjects also the fourth evoked response may be slightly smaller than the first one, but the reduction is not more than 7%. If the reduction in amplitude of the compound muscle action potential is ≥10%, the test is called positive (a decremental response). The test is more likely to be positive on testing several muscles or when a weak muscle is tested.20 For patients’ comfort, it is helpful to start by testing distal muscles first and if there is no positive response then test proximal muscles. This test is virtually always positive in generalised myasthenia gravis but may be negative in nearly 50% cases of ocular myasthenia gravis.22 Overall, sensitivity is about 75%.

Single fibre electromyography is the most sensitive test (>95%) in myasthenia gravis. In this test, the action potentials generated by closely adjacent muscle fibres of the same motor unit are recorded with a fine electrode.23 When a motor unit is activated, the action potentials reaching muscle fibres are not all synchronous. The mean interpotential difference between two fibres is called “jitter” and is normally less than 55 μsec. In myasthenia gravis, this interval or jitter is increased and is usually >100 μsec. This is due to the abnormally low and decremental EPPs in myasthenia gravis. Understandably, lower amplitude EPPs take a longer time to reach the threshold to activate action potential in muscle fibres than the normal amplitude EPPs. Some of the impulses fail to generate action potentials at one or more fibres (impulse blocking).

The limitations of the electrophysiological tests include their false positivity in any condition with a reduced safety factor at the neuromuscular junction—for example, peripheral neuropathies, polymyositis, motor neuron disease, etc. It is said that all cases of myasthenia gravis can be identified by combining results of AChR antibody test, single fibre electromyography test, and repetitive nerve stimulation test.44 47

(F) Computed tomography/MRI of chest
Computed tomography/MRI of the chest are used to screen for associated thymic tumours. There is greater yield in patients over 40 years of age. The imaging may be used post-thymectomy to look for residual thymic tissue in patients who deteriorate unexpectedly. The thymus can normally be visualised up to mid-adulthood. The persistence of a thymic shadow after the age of 40 or an enlargement of the thymus on serial scans should prompt suspicion of a thymic tumour.

Patients should be screened for the diseases known to be associated with myasthenia gravis (for example, thyroid disease, diabetes mellitus, rheumatoid disease, pernicious anaemia, systemic lupus erythematosus, sarcoidosis, Sjogren’s disease, polymyositis, etc) and for those disorders that may interfere with the immunosuppressive treatment (for example, hypertension, tuberculosis, peptic ulcer, osteoporosis, etc).

In cases where a structural or inflammatory brainstem lesion is possible, MRI of the brain may be indicated.

DIFFERENTIAL DIAGNOSIS OF MYASTHENIA GRAVIS
A number of conditions may mimic myasthenia gravis. They include other neuromuscular junction disorders (Lambert-Eaton syndrome, botulism, acquired neuromyotonia, congenital myasthenia, drug induced myasthenia gravis, etc), metabolic and toxic myopathies, and brain stem diseases (for example, ischaemic, inflammatory, and neoplastic) if myasthenia is restricted to bulbar involvement. Lambert-Eaton syndrome is an autoimmune disorder of the neuromuscular junction manifesting as muscle weakness and is often associated with the small cell carcinoma of the lung. Table 3 outlines the differentiating features of Lambert-Eaton syndrome and myasthenia gravis.

Penicillamine induced myasthenia is an autoimmune disorder and resembles myasthenia gravis. The drug history is an important part of the diagnostic evaluation of myasthenia gravis. Myasthenia recovers within weeks after the drug is stopped. Some drugs—for example, curare, amino-glycosides, procainamide, and quinine—can cause weakness in normal people and may exacerbate myasthenia gravis. However, the weakness improves when the culprit drug is stopped.

Botulism can cause generalised weakness, internal and external ophthalmoplegia, and respiratory paralysis. Pupillary involvement and the incremental, rather than the decremental, response on repetitive nerve stimulations help in differentiating it from myasthenia gravis.

Hyperthyroidism is easily excluded by thyroid function tests, which should be routinely checked in the evaluation of myasthenia gravis. Ocular myasthenia should be differentiated from progressive external ophthalmoplegia (a mitochondrial disorder), ocular Graves’ disease, and intracranial
space occupying lesions. In difficult cases, referral to a neurologist should be made.

TREATMENT OF MYASTHENIA GRAVIS

Modern treatment of myasthenia gravis is highly effective. Before 1958, it carried a mortality of around 30% despite treatment. This has been reduced practically to zero with current therapy. Unfortunately, despite advances in the treatment of myasthenia gravis, there is a paucity of evidence base. The following treatment modalities are available:

- Acetylcholinesterase inhibitors.
- Corticosteroids.
- Immunosuppressants.
- Plasmapheresis.
- Intravenous immunoglobulins.
- Thymectomy.

The treatment of myasthenia gravis can be considered to involve three steps: (1) initial treatment usually involves use of the acetylcholinesterase inhibitors. However, these drugs are usually not adequate to control disease on their own and an additional therapy is mostly needed. (2) Often an immune directed treatment is added, beginning with either thymectomy or high dose corticosteroids. (3) In the long term, steroid-sparing medications are usually added to facilitate the tapering phase. Short term therapies—that is, intravenous immunoglobulin or plasmapheresis—may be effective in the early stages of treatment, before thymectomy, or later during an exacerbation.

(A) Acetylcholinesterase inhibitors

These drugs act by inhibiting acetylcholinesterase and thus increase availability of the acetylcholine to act on the AChRs. They are usually the initial drugs used in the treatment of myasthenia gravis and may be the only drug required to treat mild disease. However, they do not modify the course of the disease and confer only symptomatic benefit. Pyridostigmine bromide is the most frequently employed drug in this class. It is often started at a dose of 30 mg three times a day and can be gradually increased to 60–90 mg four times a day based on the response and the tolerability. The main advantage of the drug is its rapid onset of effect (within 15–30 minutes). The duration of effect is about four hours. The common side effects are abdominal pain, diarrhoea, and excessive salivation. These are muscarinic side effects and can be treated by anticholinergic drugs like propantheline or diphenoxylate (Lomotil) without loss of nicotinic effect. The dosing can be tailored to the patient’s needs, for example, half an hour before meals in patients with some difficulty in swallowing.

Generally, AChR inhibitors provide only partial remission and the effects tend to diminish with continued treatment. Cholinergic crisis is a condition of too much of acetylcholine at the neuromuscular junction caused by the use of high doses of inhibitors of acetylcholinesterase. This is characterised by worsening weakness, hyper-persalivation, abdominal pains, and diarrhoea. Patients should be warned of this possibility before they are started on the pyridostigmine and should be advised to avoid taking too many tablets. Treatment entails reduction of the dose and a supportive management.

(B) Corticosteroids

Corticosteroids are needed to treat myasthenia gravis of moderate or greater severity and sometimes in mild disease that fails to respond fully to acetylcholinesterase inhibitors. As the long term use of steroids is associated with a significant risk of potentially serious side effects, it is imperative to discuss them fully with the patient before starting treatment. They should be started at a low dose (for example, prednisolone 10–20 mg/day) to avoid the early worsening noted in nearly 48% of patients on high dose regimens. The dose can be gradually increased by 5 mg every third day up to 60 mg/day. They can be used at initial high doses when symptoms are worsening rapidly, though this should be done in the hospital with close monitoring of forced vital capacity. Corticosteroids improve myasthenia gravis in the vast majority of patients. The improvement usually begins in 2–4 weeks, with maximal benefit realised after 6–12 months or more. After about three months of daily high dose treatment, the schedule is gradually modified to an alternate day regimen. The alternate day therapy has an advantage of fewer side effects, though many patients need additional steroid dose on “off” days due to the emergence of disease symptoms. The total dose is then tapered very slowly, but it may require months or years to determine the minimal effective dose. Few patients are able to do without prednisone entirely.

The side effects of steroids include weight gain, hypertension, hyperglycaemia, osteoporosis, aseptic necrosis of the hip, cataracts, immunosuppression, etc. Regular monitoring of blood pressure, blood glucose, potassium levels, and bone density is essential when using long term steroid therapy. Concurrent osteoporosis prophylactic treatment should be started as per national guidelines for the treatment and prevention of corticosteroid induced osteoporosis, particularly in older and/or immobile patients.

(C) Immunosuppressants

Because of the serious side effects associated with long term steroid treatment, use of other immunosuppressant drugs as

<table>
<thead>
<tr>
<th>Feature</th>
<th>Lambert-Eaton syndrome</th>
<th>Myasthenia gravis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of defect</td>
<td>Presynaptic</td>
<td>Postsynaptic</td>
</tr>
<tr>
<td>Component of neuromuscular</td>
<td>Voltage gated calcium channels</td>
<td>AChR on the junctional folds</td>
</tr>
<tr>
<td>junction affected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial presentation</td>
<td>Usually limb muscle weakness</td>
<td>Usually ocular weakness</td>
</tr>
<tr>
<td>Progression</td>
<td>From limbs to face</td>
<td>Cranio-caudal</td>
</tr>
<tr>
<td>Effect of exercise</td>
<td>Improves weakness</td>
<td>Worsens weakness</td>
</tr>
<tr>
<td>Common associated tumour</td>
<td>Small cell lung carcinoma</td>
<td>Thymic tumours</td>
</tr>
<tr>
<td>Deep reflexes</td>
<td>Decreased or absent</td>
<td>Intact or brisk</td>
</tr>
<tr>
<td>Autonomic disturbances</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Autoantibody in serum</td>
<td>Antibody against voltage gated calcium channels in presynaptic membrane</td>
<td>AChR antibody</td>
</tr>
<tr>
<td>RNS test</td>
<td>Incremental response</td>
<td>Decremental response</td>
</tr>
</tbody>
</table>

RNS, repetitive nerve stimulation.
“steroid sparing agents” is now common.\textsuperscript{39} Azathioprine, cyclophosphamide, cyclosporin, methotrexate and, recently, mycophenolate mofetil have been used in the treatment of myasthenia gravis. It is helpful to understand that it takes weeks to months before these drugs start to work and, therefore, they should be started concurrently with steroids. Azathioprine has been in use for a long time and its relatively favourable safety profile makes it the first choice in this class of drugs. Its effectiveness has been shown in a randomised trial.\textsuperscript{37} It is started at a low dose of 30 mg/day and if tolerated, the dose is gradually increased depending on the response. Up to 10% of the patients develop troublesome side effects such as idiosyncratic flu-like illness, bone marrow suppression, and liver toxicity. Regular monitoring of blood counts and mean corpuscular volume of red cells is warranted to detect bone marrow suppression. Azathioprine takes 3–6 months to start working. Cyclosporin has also been shown to be effective in the treatment of myasthenia gravis,\textsuperscript{38} though 35% of patients in this study could not tolerate this drug, nephrotoxicity being the main reason for discontinuation of the drug. Increase in blood pressure is another common side effect and, therefore, regular monitoring of blood pressure and serum creatinine is mandatory. Cyclophosphamide, methotrexate, and mycophenolate mofetil are other immunosuppressants used in treating myasthenia gravis. A “steroid sparing” agent. Cyclophosphamide is very toxic and mycophenolate is currently expensive. Low dose tacrolimus plus steroids has been reported to be effective in intractable disease.\textsuperscript{31}

(D) Plasmapheresis
Plasmapheresis is based on the antibody-mediated pathogenesis of myasthenia gravis, and has been used in its treatment for more than 30 years. It produces rapid but temporary improvement by reducing the amount of AChR antibodies. Various methods of plasmapheresis including double filtration plasmapheresis, immunoabsorption plasmapheresis, and plasma exchange have been used. The major indications are (a) immediate treatment in patients with serious myasthenia gravis or myasthenic crisis, (b) preparation of patients with severe myasthenia gravis before thymectomy, (c) in the early postoperative period, and (d) in cases of symptom worsening during tapering or initiation of immunosuppressive therapy. The factors predicting better clinical response are severe myasthenia gravis, absence of thymoma, early onset myasthenia gravis, and higher removal rate for IgG.\textsuperscript{54} The improvement rarely persists for more than 4–10 weeks and, therefore, immunosuppressive therapy has to be continued. Plasmapheresis requires expensive equipment and thus its availability may be a limiting factor in some places. The complications include complications of intravenous access (for example, central line placement), hypotension, and coagulation disorders.

(E) Intravenous immunoglobulin
Intravenous immunoglobulin is also shown to be effective in the treatment of myasthenia gravis, though its mechanism of action remains unknown. It has the same indications as plasmapheresis including severe myasthenia gravis or myasthenic crisis, preoperative and postoperative period, and intractable myasthenia.\textsuperscript{35, 54} In contrast to plasmapheresis, intravenous immunoglobulin does not require expensive equipment or a large bore vascular access.\textsuperscript{37} Recently, it has been shown to be effective as a long term treatment in selective cases of myasthenia gravis.\textsuperscript{34} The usual dose of intravenous immunoglobulin is 400 mg/kg for five consecutive days.

Plasmapheresis usually works quicker than the intravenous immunoglobulin therapy. A direct comparison of the two therapies showed them to be equally effective.\textsuperscript{39}

(F) Thymectomy
There are two different aspects of thymectomy in myasthenia gravis: (1) thymectomy for thymic tumours associated with around 10% of patients with myasthenia gravis and (2) thymectomy for the treatment of myasthenia gravis per se. As regards to the first indication, thymectomy should always be done, as thymic tumours are potentially locally invasive. Thymectomy as a treatment of myasthenia gravis (in the absence of thymoma) has been the practice for several years. The young age and the absence of thymoma have been shown to predict a better response in some studies,\textsuperscript{50, 53} though age did not have any effect on the response in a recent study.\textsuperscript{52} It is generally agreed that patients with generalised myasthenia gravis who are between the ages of adolescence and about 60 years should be offered thymectomy, as nearly 80%–85% of patients eventually experience improvement in their myasthenia gravis after thymectomy. It is imperative to optimise a patient’s condition before operation. Because of their potential to cause worsening of the disease, muscle relaxants should be avoided before surgery. The benefits of thymectomy usually appear months or years after the operation. In skilled hands, thymectomy has negligible risks. Therefore, it should always be performed in centres with extensive experience in the surgery, preoperative and postoperative management.

The precise mechanism of action of thymectomy is unknown, though possible explanations include removal of the source of continued antigen stimulation, removal of AChR antibody-secreting B-cells, and immunomodulation.

MYASTHENIA AND PREGNANCY
The effect of pregnancy on myasthenia gravis is variable. Approximately one third of pregnant myasthenics get better and one third get worse at some time during their pregnancy, while one third do not change. There is usually worsening of disease in the first trimester and an improvement is noted in the third trimester. Anticholinesterase medications and steroids have not been found to be associated with significant risk for congenital defects. Plasmapheresis has been carried out safely during pregnancy. Myasthenia gravis affects striated muscles and the uterus is a smooth muscle. Therefore, the obstetric complications are not very common during delivery. Only during the second stage of labour when voluntary “striated” abdominal muscles are used does myasthenic weakness become noticeable. In recent studies looking at the effects of myasthenia gravis on pregnancy and delivery, complications of artificial rupture of amniotic membranes and the rate of interventions (for example, use of forceps and caesarean sections) were noted to be greater in patients with myasthenia gravis.\textsuperscript{61, 64}

MYASTHENIC CRISIS
Myasthenic crisis is an exacerbation of myasthenia leading to paralysis of respiratory muscles that requires an urgent respiratory support. This is usually caused by infections, initial high dose steroid therapy, or an inadequate treatment. Patients should be managed in an intensive care unit. In addition to respiratory support appropriate antibiotics, fluid management, and anticholinesterase therapy are required. Plasmapheresis or intravenous immunoglobulin treatment may be required for prompt control of the disease.

PROGNOSIS OF MYASTHENIA GRAVIS
Untreated myasthenia gravis has a 10 year mortality of 20%–30%. However, with modern treatment, the prognosis is excellent with practically zero mortality. Most patients are able to live normal lives, though taking immunosuppressants for life. Myasthenia gravis associated with a thymoma, particularly in older patients, carries a poor prognosis.
Our knowledge of myasthenia gravis has vastly improved in recent years. The antibody response in seronegative disease is now better characterised with recognition of additional targets of antibody attack, for example, MuSK.6 An improved understanding of the molecular structure of the AChR has helped develop antibodies against its individual subunits for diagnostic and therapeutic purposes. In a recent study, an increased diagnostic sensitivity was obtained using anti-AChR e subunit specific antibodies compared with the conventional AChR antibody testing.66 Fab fragments of increased diagnostic sensitivity was obtained using anti-}

...}

CONCLUSIONS
Myasthenia gravis is an autoimmune disorder characterised by the weakness and fatigability of the voluntary muscles that is caused by autoantibodies against the nicotinic AChR on the postsynaptic membrane at the neuromuscular junction. Our understanding of the pathogenesis, immunology, and molecular biology of myasthenia gravis has greatly improved in the last three decades. It is almost always possible to establish the diagnosis of myasthenia gravis with the current tests. Modern treatment is highly successful and mortality of treated disease is practically zero. However, there are still important gaps in our knowledge of the origin of myasthenia gravis, the factors that contribute to chronic disease, and the way to cure the disease.71

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