

Myasthenia Gravis

What is Myasthenia Gravis?

Myasthenia Gravis (MG) is a chronic, autoimmune disease that causes muscle weakness and excessive muscle fatigue. It is uncommon, affecting about 15 in every 100,000 individuals in the UK. The disease can vary in severity and distribution of weakness between individuals, and in any one patient the symptoms fluctuate with relapses and remissions. MG can resolve spontaneously, but for most patients MG persists for life. It can be life threatening, but 90% of patients become symptom-free with modern treatments.

Who is at risk of developing MG?

MG affects all races and can develop at any age from childhood to extreme old age. Young patients are more commonly women, whereas older patients, over 50 years, are more often men. People who inherit a tendency to develop autoimmune disease are at increased risk of developing MG, so a patient with MG may have another autoimmune disease, such as diabetes or thyroid disease, or have a relative with autoimmune disease. Occasionally MG develops in patients with rheumatoid arthritis who are given the drug penicillamine. In these cases, the MG symptoms usually disappear when the drug is stopped.

Is MG hereditary?

MG is not an inherited disease and does not usually occur in families. This is in contrast to the congenital myasthenic syndromes that are genetic disorders (see below). However, it is thought that an individual's genetic make-up is one factor, of perhaps many, that leads them to develop MG, and it may occasionally be found in more than one family member.

What are the symptoms of MG?

The hallmark of MG is weakness of voluntary muscles, which gets worse with repeated or sustained use of the muscle (fatiguable muscle weakness). Symptoms fluctuate and are typically worse at the end of the day, in hot weather, during or immediately after an infection, or during menstruation. In two thirds of patients with MG, the first muscles to be affected are those controlling eye and eyelid movements, and almost all patients have involvement of these muscles at some stage. In some patients, the MG only ever involves the eye muscles (ocular MG) while in the majority there is also involvement of other muscles (generalised MG). MG itself does not cause pain, but the weakness may lead to non-specific aches and pains. For instance, neck pain may occur because of weakness in the neck muscles.

What causes MG?

MG develops in adult life as the result of a defect in the immune system. The immune system's job is to produce antibodies against bacteria and viruses. Unfortunately, it sometimes produces antibodies against "self" proteins causing "auto"immune disease. The majority of patients with MG produce antibodies against a self-protein called the acetylcholine receptor (AChR). This is found at the junction between the nerve and the muscle (the neuromuscular junction (see figure 1 & 2). It acts as a "receiver" for the chemical signal, acetylcholine that is released from the nerve when we want to use a muscle. The antibodies bind to the acetylcholine receptors on the

muscle membrane and greatly reduce their ability to receive the chemical signal. As a result the patient experiences muscle weakness which becomes worse as they repeatedly try to use the same muscle. Although we now understand how antibodies to the acetylcholine receptor cause muscle weakness, we do not know why patients with MG develop these particular antibodies. In some patients with MG, the thymus gland in the chest appears to be important in triggering the abnormal immune response.

Fig. 1 Below: The normal neuromuscular junction

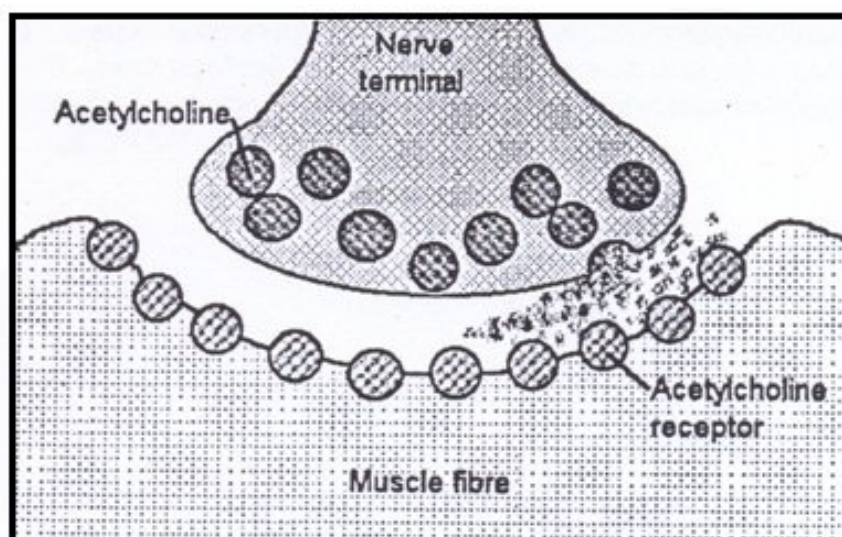
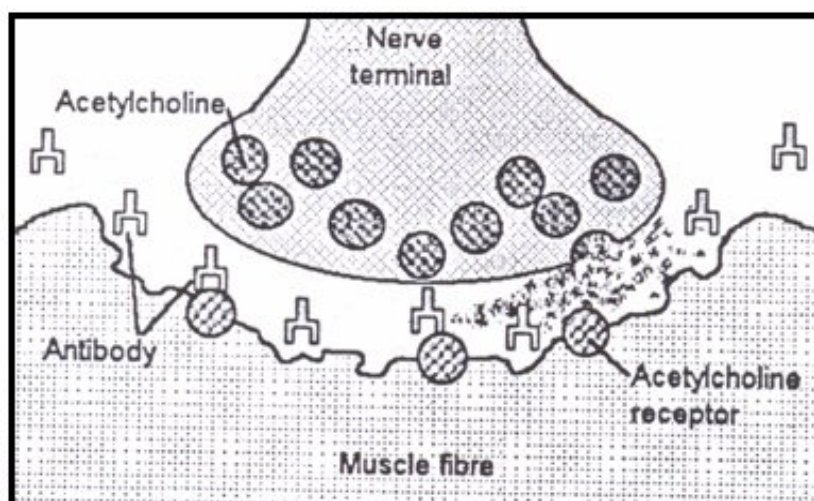


Fig. 2 Below: The neuromuscular junction in Myasthenia Gravis (MG)

The diagram shows the chemical signal, acetylcholine, and the receivers, acetylcholine receptors. The inverted Y shaped molecules are antibodies binding to the acetylcholine receptors and preventing them from working.



Is MG all the same disease?

MG presents in two main forms:

OCULAR MG affects the eye muscles only.

- 1) Drooping of the eyelids (ptosis) is often intermittent, and can affect one or both eyes
- 2) Double vision (diplopia) may be intermittent, and sometimes occurs only when looking in a particular direction.

GENERALISED MG patients usually have symptoms of ocular MG but there is also involvement of:

- 1) Face and throat muscles, affecting smiling, speech (dysarthria), chewing and swallowing (dysphagia).
- 2) Neck muscles, causing difficulties in holding the head up.
- 3) Limb muscles, causing difficulties in walking upstairs, and in holding the arms up (e.g. when brushing hair).
- 4) Breathing muscles, causing shortness of breath when exercising or when lying flat.

How is MG diagnosed?

The history and examination of the patient can suggest the diagnosis but it is important to confirm the diagnosis by special investigations:

Antibodies to the acetylcholine receptor are found in 85% of patients with generalised MG, and 50% of patients with ocular MG. They are detected by a blood test.

Electromyography (EMG) is performed by a specialist doctor and involves measuring the electrical response in the muscle with a very fine needle. An electrical stimulus is applied to a nerve and the response in the muscle is recorded. It is a very sensitive test, showing an abnormality in most patients with MG, but is not available at all hospitals.

Tensilon® test, an injection of Edrophonium is given which results in a rapid but short-lived improvement in symptoms in many patients.

Chest scan should be done to check whether the thymus is abnormal as many patients with MG have an enlarged thymus, and some have a benign tumour.

What else could it be?

The key feature that differentiates MG from many other diseases is the fatiguable character of muscle weakness and fluctuating nature of the symptoms. Diseases affecting the muscles themselves (e.g. mitochondrial cytopathy or muscular dystrophies) can cause several of the symptoms seen in MG, and the eye symptoms can present in patients with thyroid disease. There are other even rarer diseases that can be confused with MG and which are described briefly below.

What will the doctor do?

Since MG is uncommon, the General Practitioner usually refers the patient to a specialist neurologist for further assessment and tests, and for initiation of treatment. Once the diagnosis has been made the General Practitioner has a very important role in prescribing and monitoring the medication.

What can the patient do themselves?

Patients should use common sense and avoid things that would put them in danger if their weakness suddenly increased (for instance swimming on their own). Taking medications regularly is the key to maintaining the lowest possible levels of symptoms.

Can women with MG have babies?

Many women with MG develop the disease as teenagers and the disease is well controlled before they want to have children. The MG symptoms sometimes get worse during pregnancy but equally often get better. Sometimes the baby is born with a transient form of MG, due to the transfer of antibodies across the placenta, but these symptoms respond well to treatment and usually disappear within days to weeks causing no permanent disability. On very rare occasions, an untreated mother may give birth to a baby with severe symptoms, (including joint deformities) requiring intensive care. This has never been reported in a mother who has been diagnosed and adequately treated for MG.

What is the treatment?

Anti-cholinesterase medication

The first specific form of treatment is anti-cholinesterase drugs (usually one called Pyridostigmine), which prevent the breakdown of acetylcholine and so improves the efficiency of the chemical signal at the neuromuscular junction. The benefits of Pyridostigmine occur within 30-60 minutes, but wear off in 3-4 hours, so tablets should be taken at regular intervals throughout the day. Patients may develop colicky abdominal pain and diarrhoea on Pyridostigmine, because the medication also increases nerve and muscle action in the intestine. If this occurs the dose can be reduced, or alternatively Propantheline can be taken 30 minutes before each Pyridostigmine dose to counteract the effects on the bowel. For some patients MG symptoms disappear with Pyridostigmine alone, but most require additional treatments, which vary for each patient.

Thymectomy

Since the thymus can be abnormal in patients with MG, surgical removal of the thymus (thymectomy) is recommended for some patients. Following thymectomy, MG symptoms do not usually improve in patients with a thymoma, but may improve in young patients with an enlarged thymus. In these patients, approximately 1 in 4 are cured by thymectomy, 2 in 4 have significant improvement, but 1 in 4 do not improve. Improvement following thymectomy is usually apparent in the first year, but may take up to 3 years to occur. If the patient recovers, or improves significantly following thymectomy, then they may not need any additional therapy. But many patients will need further treatments.

Immunosuppression:

- **Steroids.** Patients who do not respond to thymectomy, or do not undergo a thymectomy, are treated with steroids. Patients are usually started on a low dose of steroids, which is gradually increased over the next few weeks to reach the full dose. During this period the patients are often kept in hospital as symptoms sometimes deteriorate before they

improve. Once the symptoms are controlled, the dose of steroids is gradually reduced to find the minimum dose at which the symptoms remain under control. Patients then remain on that dose.

There are several side effects associated with steroids, some of which can be prevented by taking additional medication. Thinning of the bones (osteoporosis) can occur and so patients will have a bone densitometry (DEXA) scan and will have medication to protect the bones if appropriate. Patients should never stop taking steroids suddenly, as this can result in a serious condition because the body has become used to regular steroids. All patients should carry a "steroid card" so that in an emergency other doctors will know that they require regular steroids.

- **Steroid-sparing agents.** Although steroids are extremely effective in controlling MG, there are potential side effects. Therefore, additional drugs are often used which allow the doctors to reduce the dose of steroids required and may even allow the patient to stop steroids completely. These drugs also suppress the immune system but they act in a different way to the steroids, take longer to work and have different side effects. Thus by using a small dose of steroids and one of these other medications, the side-effects are kept to a minimum, while maximising the immunosuppressive effect. Azathioprine is the only steroid-sparing agent that has been tested formally and found to be beneficial in treating MG. However in-patients who cannot take Azathioprine, alternatives such as Methotrexate or Cyclosporin appear to be effective. Patients taking steroids or steroid-sparing agents are at increased risk of infection. It is best for patients to consult their doctors before having any vaccinations (live vaccines should be avoided), or engaging in unusual activities that could put them at risk of contracting infections.

Emergency treatments

If a patient is very weak or is having trouble with breathing or swallowing then they are usually admitted to hospital for more aggressive treatments such as plasma exchange or intravenous immunoglobulin (IVIg). These treatments can produce a rapid improvement in symptoms but the benefits only last for about 6 weeks. They are reserved for situations when symptoms need to be controlled quickly, and they are not appropriate long-term treatments.

What is the prognosis?

The prognosis of MG has improved significantly with the introduction of immunosuppressive therapy. The majority of patients become symptom free if they are adequately treated. However most patients do have to remain on tablets for life as the symptoms generally return if they stop the medication.

What other diseases can be mistaken for MG?

MG is the most common of the neuromuscular junction conditions, but about 3 in 20 of patients presenting with symptoms of MG will not have antibodies to the acetylcholine receptor. Some of these will have antibodies to another muscle protein, called MuSK. **MuSK antibody myasthenia** is treated in much the same way as the usual form of MG, although thymectomy may not be needed. Some will have the **Lambert Eaton myasthenic syndrome**. In this condition, the patients are also weak and fatigue easily, but eye symptoms are less common. About half the patients are smokers and a particular type of lung cancer may be found.

Antibodies to another neuromuscular junction protein, the voltage-gated calcium channel, cause the disease. Treatment is similar to that for MG but thymectomy is not performed. There are also rare **congenital myasthenic syndromes**, which are due to hereditary gene mutations in the acetylcholine receptor. Antibodies do not cause these and thymectomy and immunosuppressive drugs are not used.

Support Group

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Updated: 04/08

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