



Myasthenia gravis

Overview

Myasthenia gravis (sometimes abbreviated to MG) is a chronic, autoimmune condition that causes muscle weakness and excessive muscle fatigue. It is rare, affecting about 15 in every 100,000 people in the UK.

The condition can vary in severity and distribution of weakness between individuals, and in an individual, the symptoms can fluctuate with relapses and remissions. Myasthenia gravis can resolve spontaneously, but for most people the condition persists for life. It can be life-threatening, but with modern treatments, 90 percent become symptom-free. Myasthenia gravis presents in two main forms, ocular myasthenia gravis and generalised myasthenia gravis.

Who is at risk of developing myasthenia gravis?

Myasthenia gravis 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 the age of 50, are more often men. People who inherit a tendency to develop an autoimmune condition are at increased risk of developing myasthenia gravis, so a patient with myasthenia gravis may have – or have a relative with – another autoimmune condition such as diabetes or thyroid disease. Occasionally, myasthenia gravis develops in people with rheumatoid arthritis who are given the drug penicillamine. In these cases, the myasthenia gravis symptoms usually disappear when the drug is stopped.

Is myasthenia gravis inherited?

Myasthenia gravis is not an inherited condition and does not usually occur in families. This is in contrast to the congenital myasthenic syndromes that are genetic conditions (see below). However, it is thought that a person's genetic make-up is one of perhaps many factors that lead them to develop myasthenia gravis, and it may occasionally be found in more than one family member.

Symptoms

The hallmark of myasthenia gravis is weakness of voluntary muscles, which gets worse with repeated or sustained use of the muscle (fatigable 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 myasthenia gravis, 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, myasthenia gravis only ever involves the eye muscles (ocular myasthenia gravis) while in the majority there is also involvement of other muscles (generalised myasthenia gravis). Myasthenia gravis 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.

Ocular myasthenia gravis affects the eye muscles only:

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

Generalised myasthenia gravis usually involves symptoms of ocular myasthenia gravis but there is also involvement of:

- face and throat muscles, affecting smiling, speech (dysarthria), chewing and swallowing (dysphagia)
- neck muscles, causing difficulties in holding the head up
- limb muscles, causing difficulties in walking upstairs, and in holding the arms up (e.g. when brushing hair)
- breathing muscles, causing shortness of breath when exercising or when lying flat.

What is the prognosis?

The prognosis for myasthenia gravis has improved significantly with the introduction of immunosuppressive therapy. Most people become symptom-free if they are adequately treated, however they do have to remain on tablets for life as the symptoms generally return if they stop the medication.

Causes

Myasthenia gravis develops in adult life as the result of a defect in the immune system. The immune systems job is to produce antibodies against bacteria and viruses. Unfortunately, it sometimes produces antibodies against 'self' proteins causing 'auto' immune disease.

The majority of people with myasthenia gravis 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 figs 1 and 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 myasthenia gravis develop these particular antibodies. In some cases, the thymus gland in the chest appears to be important in triggering the abnormal immune response.

Fig. 1: The normal neuromuscular junction

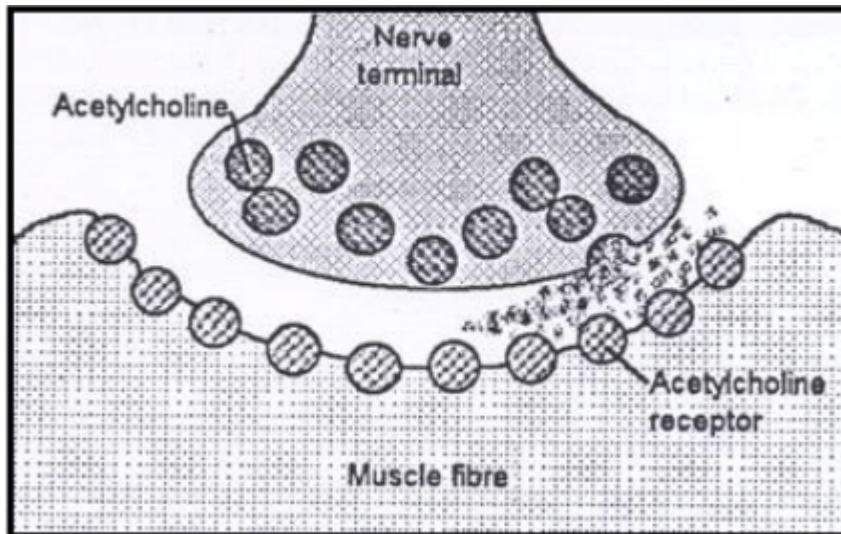
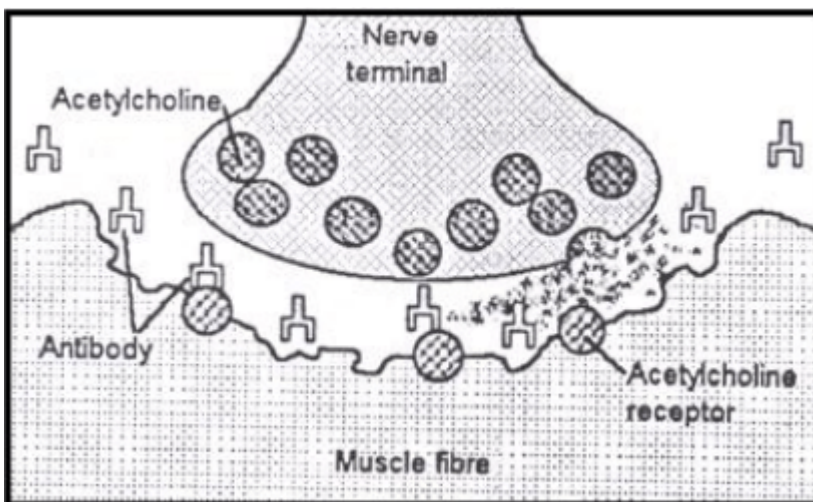


Fig. 2 The neuromuscular junction in myasthenia gravis



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.

Diagnosis

Examining the person and their medical history can suggest the diagnosis but it is important to confirm the diagnosis by special investigations.

Antibodies to the acetylcholine receptor are found in 85 percent of people with generalised myasthenia gravis, and 50 percent of patients with ocular myasthenia gravis. These 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 cases, but is not available at all hospitals.

Tensilon® test, an injection of edrophonium is given, which results in a rapid but shortlived improvement in symptoms in many patients.

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

What will the doctor do?

As myasthenia gravis is rare, the general practitioner (GP) 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 GP has a very important role in prescribing and monitoring the medication.

What else could it be?

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

What other conditions can be mistaken for myasthenia gravis?

Myasthenia gravis is the most common of the neuromuscular junction conditions, but about three in 20 people presenting with symptoms of myasthenia gravis 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 myasthenia gravis, although thymectomy may not be needed.

Some will have the Lambert Eaton myasthenic syndrome. With this condition, people are also weak and fatigue easily, but eye symptoms are less common. About half 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 condition. Treatment is similar to that for myasthenia gravis but thymectomy is not performed. There are also rare congenital myasthenic syndromes, caused by hereditary gene mutations in the acetylcholine receptor. Antibodies do not cause these and thymectomy and immunosuppressive drugs are not used.

Can women with myasthenia gravis have babies?

Many women with myasthenia gravis develop the condition as teenagers and it is well controlled before they want to have children. The symptoms sometimes get worse during pregnancy but equally often get better. Sometimes the baby is born with a transient form of myasthenia gravis, owing to the transfer of antibodies across the placenta, but these symptoms respond well to treatment and usually disappear within days or weeks and cause no permanent disability. On very rare occasions, where a mother is untreated, she 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 myasthenia gravis.

Treatment

There are a number of treatments available for aspects of myasthenia gravis.

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 improve the efficiency of the chemical signal at the neuromuscular junction. The benefits of Pyridostigmine occur within 30-60 minutes, but wear off in three to four hours, so tablets should be taken at regular intervals throughout the day. People 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, myasthenia gravis symptoms disappear with Pyridostigmine alone, but most require additional treatments, which vary from person to person.

Thymectomy

Since the thymus can be abnormal in people with myasthenia gravis, surgical removal of the thymus (thymectomy) is recommended for some. Following thymectomy, symptoms do not usually improve in patients with a thymoma, but may improve in young patients with an enlarged thymus. In these patients, about one in four is cured by thymectomy, two in four have significant improvement, but one in four does not improve. Improvement following thymectomy is usually apparent in the first year, but may take up to three years. If the patient recovers, or improves significantly following thymectomy, then they may not need any additional therapy. But many will need further treatments.

Immunosuppression

- **Steroids:** People who do not respond to thymectomy, or do not undergo a thymectomy, are treated with steroids. They 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, they 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 they require regular steroids.

- **Steroid-sparing agents:** Although steroids are extremely effective in controlling myasthenia gravis, 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 from 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 myasthenia gravis. However for those 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, so they should 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 person is very weak or having trouble 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 six weeks. They are reserved for situations when symptoms need to be controlled quickly, and they are not appropriate long-term treatments.

What can people do themselves?

It is important for people to 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.

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