EASILY MISSED?

Myasthenia gravis

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This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. The series advisers are Anthony Harnden, university lecturer in general practice, Department of Primary Health Care, University of Oxford, and Richard Lehman, general practitioner, Banbury. To suggest a topic for this series, please email us at easilymissed@bmj.com.

A previously well 78 year old man presented to his general practitioner with a six month history of double vision that was more pronounced when he was tired. His wife had also noted drooping of his eyelids towards the end of the day. Examination showed restricted eye movements (ophthalmoplegia) and fatigable ptosis. He was referred to his local neurology centre and a diagnosis of myasthenia gravis was confirmed with antibody and electrophysiological tests. A computed tomography scan of his thorax was normal and he was prescribed oral pyridostigmine.

What is myasthenia gravis?

Myasthenia gravis is an autoimmune disorder of neuromuscular transmission characterised by fatigable muscle weakness. The disorder is typically mediated by antibodies against the postsynaptic acetylcholine receptor or by antibodies against muscle specific tyrosine kinase. About 10% of patients with myasthenia gravis have a thymoma.[1] Any muscle group can be affected in myasthenia gravis, but typically patients present with ocular symptoms, namely diplopia and ptosis. Weakness then becomes generalised in about 80% of patients.[2] The most serious complication is myasthenic crisis: acute respiratory failure resulting from myasthenia gravis that requires mechanical ventilation. Myasthenic crisis occurs in about 20% of patients with myasthenia gravis and is a neurological emergency requiring admission to an intensive care unit for respiratory support.[3]

Why is myasthenia gravis missed?

The fluctuating nature of the symptoms and the often subtle findings on clinical examination can make myasthenia gravis difficult to diagnose. In one study, diagnosis was delayed for more than five years in 13% of patients, and 26% of patients had had an inappropriate non-specific investigation before diagnosis.[8] The symptoms of myasthenia gravis are confined to the eye in about 20% of patients with the condition, which can make diagnosis challenging.[2]

Myasthenia gravis may be under-recognised in elderly people, partly because symptoms such as dysphagia, fatigue, and slurred speech can have a broad differential diagnosis in that group.[9] Myasthenia gravis has been reported to have been mistaken for stroke, Parkinson's disease, and motor neurone disease in elderly people.[9-11] Signs such as ptosis may also be attributed to aponeurotic ("age related") ptosis (so called because of the stretching of the aponeurosis tendon, which generally occurs in older people).

A diagnosis of myasthenia gravis may be missed in primary and secondary care as some patients may have negative serology results (antibodies) and normal electrophysiology, particularly if they have only ocular myasthenia gravis.[12] Thus a thorough history is central to the diagnosis.

KEY POINTS

- Suspect myasthenia gravis in patients with fluctuating weakness, which initially is typically ocular, although weakness subsequently becomes more generalised in 80% of patients
- If myasthenia gravis is suspected, refer the patient to a neurology centre for investigations, including testing for the presence of antibodies to the acetylcholine receptor and to muscle specific tyrosine kinase, and specific electrophysiological tests
- The patient may still have myasthenia gravis even if the results of serology and electrophysiological investigations are normal; history is key to the diagnosis
- Effective treatment (including acetylcholinesterase inhibitors and steroids) is available for this potentially fatal condition and should not be discontinued abruptly; patients having surgery or experiencing other stresses need close monitoring and possibly changes in treatment to prevent myasthenic crisis

HOW COMMON IS MYASTHENIA GRAVIS?

- The prevalence of myasthenia gravis in the United Kingdom is estimated at about 15 per 100 000 population, although this figure has increased over time[4 5]
- The incidence is bimodal, with a female:male ratio of 2:1 in younger adults and a reversed sex ratio in older people[6]
- Both the incidence and the prevalence of myasthenia gravis in older patients are greater than previously thought[7]

Why does it matter?

Myasthenia gravis is eminently treatable. Untreated patients are at risk of having an acute deterioration of their symptoms and developing myasthenic crisis.

How is it diagnosed?

Clinical

History

The clinical hallmark of myasthenia gravis is fatigable muscle weakness. The history should elicit the pattern and severity of the weakness and any fluctuation of symptoms. Symptoms are typically worse at the end of the day. They may also worsen with heat, infections, surgery, or emotional stress, menstruation, pregnancy, and the post-partum state. Diplopia and ptosis are the most common presenting features of myasthenia gravis, but about 80% of patients will subsequently develop more generalised weakness.[2] Weakness is typically more noticeable in the upper limbs than the lower limbs and is often proximal. Bulbar weakness can manifest as difficulty in chewing or as slurred speech, particularly after a long conversation. Dysphagia, choking, or nasal regurgitation of liquids can herald more severe bulbar weakness. Neck weakness can lead to head drop and neck pain. Respiratory weakness may manifest with exertional dyspnoea or orthopnoea.

Examination

Cranial nerve examination may show ophthalmoplegia or weakness of forced eyelid or mouth closure. Bulbar weakness may be evident if the patient develops dysarthria or

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- Klinefelter's syndrome (*BMJ* 2012;345:e7558)
- Perilunate dislocation (*BMJ* 2012;345:e7026)
- Hirschsprung's disease (*BMJ* 2012;345:e5521)
- Pre-eclampsia (*BMJ* 2012;345:e4437)
- Post-traumatic stress disorder (*BMJ* 2012; 344:e3790)

nasal speech after prolonged speaking, such as at the end of the consultation or after counting to 50. Fatigability can be elicited by watching for the development of ptosis during sustained upgaze. On examination of the peripheral nervous system, fatigability can be assessed by testing shoulder abduction before and after unilateral repetitive arm movement. There may be obvious weakness of neck flexion or extension, and if diaphragmatic weakness is present, there may be paradoxical abdominal movement during inspiration.

Investigations

Ice test

If the diagnosis of myasthenia gravis is suspected, refer the patient to a neurology unit for further investigations. In patients with ptosis, the ice test is a simple first line test that can be done in the clinic while waiting for other investigations. This distinguishes myasthenia gravis from other causes of ptosis and involves application of crushed ice in a latex glove to the eye for three minutes. In myasthenia gravis this leads to improvement of ptosis and has a sensitivity and specificity of >90%.[13]

Laboratory investigations

The presence of antibodies to the acetylcholine receptor or to muscle specific tyrosine kinase is highly specific. About 85% of patients with generalised myasthenia gravis have antibodies to the acetylcholine receptor, and 40-70% of the rest are positive for antibodies to muscle specific tyrosine kinase.[14] Repeating negative serological tests can be useful because a seroconversion rate of 15% over one year has been reported.[14] Nevertheless, some patients will be persistently seronegative, especially those with only ocular myasthenia gravis.[12]

Levels of muscle specific enzymes such as creatine phosphokinase are usually normal in myasthenia gravis.

Neurophysiology

Routine electrophysiology generally yields normal results in myasthenia gravis, and the diagnosis may be missed if specific electrophysiological tests such as repetitive nerve stimulation and single fibre electromyography are not requested. Repetitive nerve stimulation is specific for myasthenia gravis, but the sensitivity is only 70% and is even lower in disease that is purely ocular.[12] Single fibre electromyography is a selective recording technique that allows identification of action potentials from individual muscle fibres. It is more sensitive (92-100%) than repetitive nerve stimulation for myasthenia gravis but is not specific.[15] Single fibre electromyography is a challenging technique that depends greatly on the skill of the operator and the muscles that are tested as often only affected muscles will show positive results.

Edrophonium test

The edrophonium (Tensilon) test involves intravenous administration of a short acting acetylcholinesterase inhibitor while watching for a transient improvement in muscle strength.[16] The test should be done only when an objective improvement in muscle strength, such as resolution of ptosis, can be shown. Although it has a high sensitivity (95%) for generalised myasthenia gravis, it is now rarely done as it can result in life threatening bradycardia and requires immediate access to resuscitation facilities.

RED FLAGS FOR AN IMMINENT MYASTHENIC CRISIS
- Rapid worsening of primary myasthenic symptoms
- Rapid progression of bulbar symptoms
- Increasing dose of pyridostigmine
- Tachypnoea
- Tachycardia
- Decreased forced vital capacity
- Respiratory infection

Radiology

Although it does not form part of the diagnostic tests, computed tomography of the thorax is required in all patients in whom myasthenia gravis is diagnosed to exclude the presence of an underlying thymoma.

How is myasthenia gravis managed?

Acetylcholinesterase inhibitors, such as pyridostigmine, provide short lived symptomatic relief and are first line treatment, although they are less useful in myasthenia gravis when patients have antibodies to muscle specific tyrosine kinase.[17] Most patients will require immunomodulatory therapy, started by secondary care.[18] Oral steroids are generally first line immunosuppressive treatment, although side effects limit long term use.[17] High initial doses of prednisolone can transiently exacerbate weakness, and patients may be admitted to hospital if rapid escalation of treatment is needed.[18] Second line immunosuppressive agents used in myasthenia gravis include azathioprine, mycophenolate mofetil, methotrexate, tacrolimus, and ciclosporin.[17] Rituximab has been used in severe treatment resistant myasthenia gravis.[19] Intravenous immunoglobulin and plasma exchange are reserved for rapidly deteriorating myasthenia gravis and for the treatment of myasthenic crisis.[18]

Thymectomy is a well recognised treatment for myasthenia gravis and should always be performed if a thymoma is suspected.[17 18] Thymectomy is also considered in non-thymomatous generalised myasthenia gravis in patients with antibodies to the acetylcholine receptor who are aged under 50.[18] Thymectomy is not generally carried out in myasthenia gravis when patients have antibodies to muscle specific tyrosine kinase, late onset myasthenia gravis, or purely ocular disease.[18]

Importantly, patients should not abruptly discontinue their treatment for myasthenia gravis. Patients who are dysphagic and cannot take oral medication should be admitted to hospital and other routes of administration, such as nasogastric tubes, should be sought. Moreover, patients who are septicaemic, having surgery, or experiencing some other stress require close monitoring because a change or escalation of their treatment may be needed to prevent myasthenic crisis. Some medications—such as aminoglycoside and quinolone antibiotics, quinine, and intravenous magnesium—are contraindicated in myasthenia gravis as they can impair neuromuscular transmission. A full list of medications that can affect myasthenia gravis is available from the Myasthenia Gravis Foundation of America (www.myasthenia.org).

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10-MINUTE CONSULTATION

Minor incised traumatic laceration

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This is part of a series of occasional articles on common problems in primary care. The *BMJ* welcomes contributions from GPs.

A 40 year old man consults with a minor laceration of the left arm. He cut himself with a knife while working in the garden. He has washed the wound and the bleeding has stopped.

What you should cover

Medical history

- Minor incised traumatic lacerations often happen during daily household activities, while working, and while doing sports and hobbies.
- Explore the mechanism of injury and consider the possibility of contamination of involved surfaces or instruments. Ask about the time of the laceration and about subsequent cleansing and disinfecting.
- Explore risk factors for potentially compromised wound healing, such as diabetes mellitus, use of immunosuppressive medication, peripheral vascular disease, bleeding diathesis, and history of keloid formation or scar hypertrophy.
- Ask the patient's preference for method of wound closure. Most lacerations can be managed in primary care; closing methods include transcutaneous or intracutaneous sutures, adhesive (cyanoacrylate) glue, or adhesive plasters.
- Inform the patient about risk of infection, pain during the procedure, and scarring. Obtain and record informed consent.

What you should do

Physical examination and wound cleansing

- Inspect thoroughly the size, edges, and depth of the wound, particularly focusing on damage to the underlying and surrounding tissue, the vitality of the wound, and contamination. Check motor and sensory function distal to the wound, as well as circulation (pulses, capillary refill). Assess for tendon damage by checking movement and range of motion, especially for lacerations on extremities. Localised sharp pain when a wound is palpated is a useful indicator of a possible foreign body.
- Refer the patient to a surgeon if you diagnose or suspect musculotendinous injury; if the wound is more likely to result in a poor cosmetic outcome (such as crossing the lip, nose, or ear); or if you cannot establish the extent of damage to the underlying tissue.
- Profusely irrigate and cleanse the wound with tap water or sterile saline solution (neither is superior in terms of infection risk). Debride possible devitalised tissue, disinfect, and ensure haemostasis. Keep hair out of the wound. Use clean, non-sterile gloves. Evidence shows that using non-sterile gloves does not result in higher risk of infection than using sterile gloves. Do not close wounds with active signs of infection, but consider secondary closure after three to five days.

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- Adult trigger finger (*BMJ* 2012;345:e5743)
- Myalgia while taking statins (*BMJ* 2012;345:e5348)
- Otitis externa (*BMJ* 2012;344:e3623)
- Blood stained nappy (*BMJ* 2012;344:e3496)

- Minor incised traumatic lacerations (≤5 cm) without signs of infection and no tendon injuries can be closed immediately (the Friedrich dogma that wounds older than six hours must not be closed is based on tests in guinea pigs in 1898). Properly disinfected lacerations may be closed up to 24 hours afterwards.

Wound closure

Adhesive glue and sutures have comparable cosmetic outcomes for minor incised lacerations ≤5 cm in adults and children treated by primary care doctors. The use of adhesive glue involves considerably less time for the doctor and less pain for the patient. Furthermore, economic analyses show that absorbable sutures are 2.4 times more expensive than adhesive glue and that non-absorbable sutures are 6.8 times more expensive. Adhesive skin glue was developed especially for skin closure and has been used extensively since the 1970s; several brands and types of applicators are available, with the most common being cyanoacrylate polymers packed in either single use vials or larger packages. The most recent Cochrane review of nine trials and 834 lacerations shows that adhesive glue has a slightly higher dehiscence rate (risk difference 2.4% (95% confidence interval 0.1% to 4.9%); number needed to harm 40) but fewer incidences of erythema (−10% (−19 to −0.4); 10). There is no risk difference for infections (overall risk 1.1%) Adhesive glue should not be used on mucosal surfaces, in areas with dense natural hair, or in areas of high tension or repetitive movements, such as joints or the posterior trunk. Choose adhesive plasters only in cases of very small, tension-free wounds.

Sutures

Use infiltration anaesthesia with an appropriate anaesthetic. Slow injection by a small needle (>20 gauge) will minimise the pain of infiltration. Avoid vasoconstrictors (for example, epinephrine) in areas with end organ blood supply, such as fingers, nose, and toes. Consider cutting away any jagged edges of the wound and devitalised tissue. Choose the size, material, and technique of the sutures according to the location (table) and depth of the wound, while bearing in mind the differences in pulling strength and tissue reaction. Choose absorbable sutures in areas where suture removal would be difficult.

Size of suture and length of time until removal of sutures for different anatomical locations

Location	Suture size*	Time until suture removal (days)
Face	5-0 or 6-0	3-5
Scalp	4-0	7-10
Chest	4-0 or 3-0	7-10
Extremities	4-0 or 3-0	7-10
High tension area (joints) and back	3-0 or 2-0	10-14

*Defined by the US Pharmacopeia.

Most lacerations can be closed using simple, interrupted, transcutaneous, non-absorbable sutures. Of these, synthetics have the least tissue reactivity, and monofilaments or braided materials may be used. The smaller the suture (note that "4-0" or "0000" is smaller than "3-0" or "000"), the lower the tensile strength of the strand. Sutures should exert minimal tension on the tissues and must be locked firmly.

Adhesive glue

Avoid applying adhesive glue to the subcutis or base of the wound. Apply glue only to the epidermal surface, while manually approximating the wound edges. Warn the patient of an exothermic reaction as the glue polymerises. Hold the margins together for several seconds until dry.

Wound dressing, patient advice, and follow-up

- Seal the sutured or glued wound with a bandage or absorbent dressing with an adhesive border. Advise the patient to minimise water contact for the first 24 hours, after which showering is allowed. Consider a waterproof dressing during activities that may contaminate the wound. Advise the patient to keep the wound clean and not to rub or scratch, as dehiscence may result.
- Check tetanus vaccination status and consider a booster or revaccination, according to local protocols. Consider prescribing antibiotics, according to local protocols (such as co-amoxiclav 625 mg three times daily for seven days), to patients with a laceration at very high risk of infection and to immunocompromised patients.
- With sutures, ask patients to return after five to 14 days for removal of stitches, depending on the location and the tension on the wound (table). Generally the greater the tension across a wound, the longer the sutures should remain in place. With adhesive glue, tell patients that the film will fall off by itself.
- Explain that it may take up to a year to know the final cosmetic appearance of the scar. Advise the patient to seek medical attention if the wound shows increasing redness, purulent discharge, or swelling or if he or she develops a fever.

USEFUL READING

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