Myasthenia gravis in the elderly

Myasthenia gravis is the most common neuromuscular disease. In elderly people it is often misdiagnosed as transient ischemic attack or stroke because of their shared symptoms, including muscle weakness, fatigue, and speech and swallowing disturbances. Here, we report on a case of delayed diagnosis that led to myasthenia crisis, and review the differential diagnosis and management of the disease.

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The annual incidence of myasthenia gravis is 9–10 cases per 1 million population[1] and the prevalence in the UK is 15 cases per 100,000 population.[2] Myasthenia gravis (MG) occurs in all ethnic groups and can occur at any age. Women are affected more often than men in a ratio of 3:2.[2] The condition is common in women in the fourth to fifth decades of life and in men in the sixth and seventh decades.[2] As age advances, both genders become equally affected.[2] Neonatal MG is a well known occurrence and usually transient.

Symptoms

The most common symptoms of MG are fatigue and muscle weakness. MG may affect any skeletal muscles, but ocular muscles (ocular MG), facial muscles and bulbar muscles (bulbar MG) are most frequently affected. Bulbar muscles control speech, swallowing, and breathing. Bulbar MG presents as difficulty speaking, swallowing, nasal regurgitation, breathing and respiratory stridor. Other symptoms include:

- Diplopia
- Dysarthria
- Dysphagia
- Shortness of breath
- Unsteady gait
- Difficulty in holding the head upright.

Diagnosis

Delayed diagnosis of MG is not unusual because the symptoms can be transient and variable and because weakness is a symptom of many other clinical conditions. MG can be misdiagnosed as stroke, myotonic dystrophy, Lambert-Eaton syndrome and botulism. A stepwise approach to diagnosis is useful.

A detailed history of symptoms including their duration is important. Usually the initial complaint is specific muscle weakness rather than generalised weakness. Ask about the fluctuant nature of the muscle weakness. The weakness of MG often becomes more severe as the day progresses. Take careful physical and neurological examinations. Muscle weakness may be demonstrated by repeated shoulder abduction or hip flexion.[3] Fatigue can be demonstrated by ptosis on upward gaze and eye drift on lateral gaze;[1] it may be unilateral or bilateral. Look for extraocular muscle involvement.

Box 1: Factors that can precipitate MG symptoms

- Emotional stress
- Surgery
- Immunisation
- Infection
- Metabolic disturbances
- Beta-blockers
- Calcium channel blockers
- Quinine
- D-penicillamine
- Aminoglycosides
- Ciprofloxacin
- Alpha interferon

Superior rectus or medial rectus involvement is common.[2] Inferior rectus involvement is rare, but if present it raises the suspicion of myasthenia gravis.[2] Demonstrate muscle weakness brought on by activity without any evidence of sensory impairment. Antibody tests can confirm the diagnosis of MG in patients who display clinical features.

Anti-acetylcholine receptor antibodies

Anti-acetylcholine receptor antibodies (AChR Abs) are considered the gold standard investigation.[3] Most patients (85–90%) with generalised MG have abnormal levels of AChR Abs, especially elderly patients and patients with bulbar symptoms.[1] Only 50% of patients with ocular MG have positive AChR Abs.[1]

Muscle-specific tyrosine kinase antibodies

Muscle-specific tyrosine kinase antibodies are present in 40–50% of patients with generalised MG who are seronegative for AChR Abs. Muscle-specific tyrosine kinase antibodies are not found in ocular MG or in patients with AChR Abs. Further tests are required to confirm the diagnosis of MG in patients without positive antibody tests.

Tensilon (edrophonium) test

The tensilon test is useful in patients who have negative antibody test results and have predominantly ocular signs.[3]

Edrophonium is a short-acting anticholinesterase. Intravenous administration of edrophonium temporarily blocks breakdown of acetylcholine and increases levels available at the neuromuscular junction. This leads to improvement in muscle weakness in MG patients.

Resuscitation facilities should be available when performing the test. Caution is needed when treating elderly patients as complications, such as cardiac arrhythmias, respiratory failure and seizures,[3] are common.

Edrophonium also produces symptoms such as abdominal cramping, watering of eyes, and twitching of eyelids.[3] These symptoms can be prevented by prior administration of atropine.[3]

After checking muscle strength, the initial dose (2mg) of edrophonium is injected intravenously. Watch for adverse effects, inject the second dose (8mg) of edrophonium half a minute later, and then repeat muscle strength testing. Objective improvement in ptosis, increase in the range of eye movements and improvement in limb strength each indicate MG.

The tensilon test can give false positive and false negative results. For instance, improvement may be seen in motor neuron disease and mitochondrial chronic progressive external ophthalmoplegia.[3] Also, some patients with MG do not respond to edrophonium.[3]

Electromyography

Repetitive peripheral nerve stimulation leads to a decremental response in compound action potentials in patients with MG. The test indicates MG if there is more than a 10% drop in action potential between the first and fifth responses.[3] The test also helps

Box 1: Case study

A 72-year-old woman with a history of hypertension and type-2 diabetes was referred with speech and swallowing problems to a stroke clinic. She had been treated clinically as having had a stroke. However, a CT scan of her brain and carotid Doppler were normal. Her swallowing problems became progressively worse but barium investigations were normal. She was referred to ophthalmology for bilateral ptosis, for which she had ptosis correction surgery. Two years later she was referred back to the stroke clinic with worsening symptoms, and the possibility of MG was raised. Acetylcholine receptor antibody levels were strongly positive at 27·5nM (normal range 0–0·2nM). She was admitted to hospital and commenced on pyridostigmine.

She deteriorated rapidly with shortness of breath and was then transferred to the intensive treatment unit (ITU) for respiratory support and was intubated. She received 5 days of intravenous immunoglobulins along with pyridostigmine. She was commenced on prednisolone for longer-term immunosuppression and given osteoporosis prophylaxis. Her recovery was complicated by pneumonia and uncontrolled diabetes due to steroids. Her symptoms gradually improved on high-dose steroids, and she has now been stabilised on azathioprine with tapering of prednisolone. A chest CT showed no evidence of thymoma.

differentiate MG from Lambert-Eaton myasthenic syndrome in which the muscle potential is initially small but progressively enlarges after maximal stimulation. Patients with ocular MG may have a negative result on electromyography.

Single fibre electromyography

Single fibre electromyography is a more sensitive test for MG and can help identify patients with ocular disease. It records action potentials from single muscle fibres in a motor unit, which can show a jitter phenomenon in MG patients. Jitter phenomenon occurs to a lesser extent in neuropathies and motor neurone disease.

Further tests

Once the diagnosis is confirmed, the following investigations should be performed.

Chest CT/MRI

Thymus screening is important to look for thymoma in antibody positive patients. If present, thymoma should ideally be removed in case it is locally invasive. Chest X-ray alone is not enough to detect thymoma.

Thyroid function tests

Both hypo- and hyperthyroidism are common in people with MG and can exacerbate the condition.[3] It is important to repeat thyroid function tests in patients who relapse.[3]

Spirometry

Monitoring forced vital capacity (FVC) and forced expiratory volume in 1 second is important to predict myasthenia crisis in patients with suspected respiratory distress.

Patients with an FVC<1·5L should be managed in a high-dependency unit and the ITU team needs to be informed. In suspected respiratory distress patients, it is mandatory to measure arterial blood gases. In the presence of hypoxaemia and CO_2 retention, patients should be transferred to ITU.

Management

Once the diagnosis of MG is confirmed, a neurologist best initiates medical treatment. It is important to discuss with the patient and his or her carers the long-term nature of treatment and potential side effects. Tell the patient about support groups, such as the Myasthenia Gravis Association (www.mgauk.org).

At first, symptoms may be controlled with a cholinesterase inhibitor (ChEi) such as pyridostigmine. Patients are usually then maintained using immunosuppression.

Cholinesterase inhibitors

Cholinesterase inhibitors are considered the basic treatment of MG, and pyridostigmine is the most commonly used. Usually symptoms improve within an hour of ChEi treatment, and improvement lasts for up to six hours.[2] Pyridostigmine should be started at a low dose, such as 15mg q.i.d., and gradually increased to avoid side effects. This can be increased every two days in 60mg/day increments up to the maximum of 360mg/day in divided doses.

Side effects are mainly gastrointestinal (diarrhoea, abdominal cramps) and improve when propantheline (15mg) is given with each dose of pyridostigmine.

The maximum amount of pyridostigmine should be restricted to 360mg/day to prevent cholinergic crisis.[4] Excessive dosage of ChEi can impair neuromuscular transmission and precipitate cholinergic crisis by causing depolarising block. Pyridostigmine should be withdrawn gradually over 2–4 weeks once patient symptoms are under control.

Immunosuppressants

Steroids are usually used to maintain remission, but can also be used alongside ChEis to rapidly control symptoms and if the dose of pyridostigmine exceeds 360mg/day. Steroids should be started at a low dose and gradually increased.

Other treatments such as azathioprine, methotrexate, ciclosporin, and mycophenolate are used as steroid-sparing drugs.

Prednisolone

Prednisolone is the most commonly used steroid in generalised MG. The usual starting dose is 10mg prednisolone on alternate days, which is increased gradually (maximum dose 1·5mg/kg) until symptoms are controlled.

Patients should be admitted and monitored closely during initiation because of the theoretical risk of clinical deterioration after starting steroids. Once symptoms are controlled, the dose should be reduced to the minimum required to maintain remission.

Patients should be warned about side effects such as

infections, mood changes, psychosis, osteoporosis and peptic ulcers. Gastric protection with a proton pump inhibitor should be started alongside the steroids.

Osteoporosis prophylaxis with bisphosphonates and vitamin-D and calcium should be initiated.

In well-controlled cases, prednisolone should be withdrawn over months and the patient managed using azathioprine alone. In cases of relapse, the underlying cause (infection, drugs, metabolic disturbances, stress and reduced immunosuppression) should be treated. In cases of minor relapse, prednisolone should be increased.

Key points:

- Myasthenia gravis is quite a rare autoimmune disorder
- It should be considered in elderly people with unexplained bulbar symptoms
- Most patients also develop some form of fluctuating weakness
- Diagnosis is based on clinical features, antibody tests and further investigations including electromyography
- Cholinesterase inhibitors are the basic treatment
- Steroids such as prednisolone are usually used for maintenance therapy; they can be used alongside cholinesterase inhibitors for rapid control of symptoms
- Failure to identify myasthenia gravis early may lead to myasthenia crisis.

Azathioprine

Azathioprine is the most commonly used steroid-sparing immunosuppressant. It has a proven beneficial role in treating MG, and can be given alongside prednisolone to control symptoms. Azathioprine is metabolised by the thiopurine methyltransferase (TPMT) enzyme, levels of which should be checked before initiating the treatment. Patients with low TPMT levels are prone to develop serious side effects like myelosuppression and hepatitis even with low doses of azathioprine.

Patients with normal TPMT levels can also develop side effects, so regular monitoring of full blood count and liver function is important.[4] The usual starting dose is 25mg s.i.d., which is increased by 25mg each day until the target dose, of 2.5mg/kg/day, is reached.[2] To avoid side effects, the dose should be divided into a b.i.d. regime. Usual side effects are nausea, vomiting, and diarrhoea.

Intravenous immunoglobulins and plasmapheresis

Plasmapheresis with intravenous immunoglobulins is used as rescue therapy in severe progressive cases of MG but the effects are temporary (6–8 weeks).[4] Treatment helps improve symptoms while other therapies take effect. The main indications are: myasthenia crisis, myasthenia relapse and severe weakness in a newly diagnosed patient.[4] Immunoglobulin A (IgA) deficiency should be excluded before starting therapy. Otherwise IgA-depleted immunoglobulins should be used. Some patients may develop aseptic meningitis following intravenous immunoglobulins. This usually settles within a week of stopping the treatment.

Thymectomy

Thymectomy is advised in patients with radiological evidence of thymoma except for the elderly (>75 years). In elderly patients, monitoring may be appropriate unless thymoma causes local and intrathoracic complications.[4] Thymectomy is advised even without thymoma in young patients (<45 years) with generalised MG[4], who are also positive for AChR Abs.

Prognosis

The majority of people remain free of symptoms on adequate doses of medication. More than 90% can lead a near normal life with treatment; less than 5% have persistant symptoms.[3]

We have no conflicts of interest

References

1. Schon F, Drayson M, Thompson RA. Myasthenia gravis and elderly people. *Age Ageing* 1996; **25**: 56–8
2. Shady Awwad MD, Raid Ma'luf MD, Nicolas Hamush MD, http://emedicine.medscape.com/article/1216417-treatment, (accessed 23 March 2010)
3. Hilton-Jones D. Diagnose Myasthenia Gravis, *Practical Neurology* 2002; **2**; 173-177. doi:10.1046/j.1474-7766.2002.05056.x
4. Hoch W, McConville J, Helms S et al. Autoantibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acteylcholine receptor antibodies. *Nat Med* 2001; **7:** 365-8