

Diagnosis and management of myasthenia gravis

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Myasthenia gravis is an autoimmune disorder of neuromuscular junction transmission (Vincent 2020). Clinical features are of muscle weakness, causing double vision (diplopia), drooping eyelids (ptosis), and difficulty with talking, swallowing, breathing, and walking. Myasthenia gravis is named for the muscle weakness (myasthenia) and severity (gravis). Fifty years ago mortality in myasthenia gravis crisis was estimated to be between 50% and 20%. Today this is less than 5%, related to improved intensive care and respiratory management, new immunomodulatory therapies, and importantly improved anticipatory management and early hospital admission (Alshekhlee 2009).

Myasthenia gravis is relatively rare, with an approximate annual incidence of 1 per 100,000 population, and prevalence of 15 per 100,000 population. In most patients (85%) the cause is the development of antibodies to the acetylcholine receptor at the postsynaptic neuromuscular junction, causing impaired signal transmission, and a fatiguing weakness. A smaller number of patients have antibodies to Muscle-Specific-Kinase (MuSK) that is required for the formation and maintenance of the neuromuscular junction, or do not have detectable antibodies.

How do patients with myasthenia gravis present in primary care?

Most frequently myasthenia gravis develops in women under 40, and men over 60, but may occur at any stage. An ocular presentation may include fatiguing ptosis or diplopia. Typically symptoms fatigue (that is physical power of the muscle deteriorates rapidly with repeated activity), and become more noticeable

as the day progresses. More generalized symptoms include fatiguing difficulty with speech or swallowing. There may be fatiguing weakness of the arms and legs. Difficulty with breathing is a serious problem, and development of pneumonia related to aspiration may occur.

How should patients be examined and assessed?

The patient may present with drooping of the eyelids as the day progresses, and may have pictures of their eyelids before the development of symptoms.

Diplopia may be detected on examining the patient's eye movement, and more extreme limitations of eye movement may be detected. The fatigue of the eyelid may be demonstrated by asking the patient to look upwards continually for 20 seconds, and similarly fatigue of the extraocular muscles by sustained gaze in one direction. Much is made of the ice pack test, where ptosis may be precipitated by placing an eye pack over the eye, but not likely to be practical in a general practice consultation.

Fatigue of the limbs may be demonstrated by testing arm abduction strength at rest, and testing again after 20 voluntary arm abductions at the shoulder.

Fatigue of speech may be demonstrated by asking the patient to count to 100, and observing reduction in volume and clarity of speech. Detection of breathlessness, if not due to other causes, is potentially an emergency.

Other autoimmune conditions are more common in patients with myasthenia gravis, and thyroid dysfunction may exacerbate the myasthenia. Blood tests not specific to myasthenia gravis include thyroid function and B12.

How should diagnosis be confirmed?

The diagnosis will usually be confirmed by referral to a neurologist. In some patients the diagnosis may be readily apparent on examination, and treatment commenced at the first consultation. Further investigation is appropriate. Blood tests include acetylcholine receptor antibody assay, and if negative proceeding to antiMuSK antibodies.

Electrodiagnostic studies may be supportive, and especially helpful in uncertain cases. These include repetitive stimulation study. Essentially a repetitive electrical stimulation is applied to a single muscle, and the amplitude of the compound muscle action potential measured. In myasthenia gravis there will be a decrement of the amplitude on repeated stimulation, as a reflection of the progressively impaired conduction at the neuromuscular junction, and consequent fatigue. A single fibre EMG study may also be performed, and jitter or instability of the neuromuscular junction transmission should be detected. An ice pack test may be used in a patient with ptosis. The ice pack is applied to the upper eyelid for 2 to 5 minutes, and an improvement in ptosis by 2mm or more is considered a positive test. An edrophonium (or Tensilon) test is occasionally used where there is doubt. Edrophonium, a very short acting acetylcholinesterase inhibitor, is administered intravenously and an improvement in signs is a positive result.

The main clinical presentations are ocular myasthenia (presence of any ocular muscle weakness, may have weakness of eye closure, but no other weakness), and generalized myasthenia gravis. Most patients with ocular myasthenia develop generalized myasthenia within three years. Patients with MuSK antibodies may have a different clinical presentation, especially bulbar (speech and swallowing) presentation, and altered response to treatment. Children may present with juvenile myasthenia gravis.

Having established a diagnosis of myasthenia gravis, an MRI or CT scan of the thymus is performed, looking for possible thymoma that may be associated.

If the patient has respiratory symptoms, pulmonary function tests may be important.

Other rarer myasthenic conditions to distinguish include Lambert-Eaton myasthenic syndrome (where the antibody is to the presynaptic voltage-gated calcium channel, and often associated with small cell lung carcinoma), and congenital myasthenic syndromes (these are a result of mutations in genes for neuromuscular junction proteins, and do not have an autoimmune basis).

Organophosphate poisoning from insecticides destroys the acetylcholinesterase, and botulism prevents the presynaptic release of acetylcholine, at the neuromuscular junction, causing acute presentations of neuromuscular junction dysfunction. A wider range of neurological and neuromuscular conditions may also present with fatigue and weakness, but are usually more readily distinguishable.

What are the potential complications?

The potential complications relate to muscle fatigue, especially respiratory insufficiency and swallowing difficulties. In a patient with progressive respiratory insufficiency urgent hospital admission may be needed. The deterioration may be referred to as a myasthenic crisis (a worsening of myasthenic weakness requiring intubation or noninvasive ventilation to avoid intubation), and anticipated by an impending myasthenic crisis (a rapid clinical worsening that could lead to crisis in the short term, days to weeks).

Approximately 20% of patients with myasthenia gravis experience a crisis in their lifetime, typically within two years of diagnosis. An impending crisis will probably require hospital admission for assessment, observation of respiratory and bulbar function, and ready access to an intensive care unit. Myasthenic crisis requires urgent and direct admission to an intensive care unit. Deterioration may be triggered by a respiratory or other infection. A number of drugs, including aminoglycosides such as gentamicin, and beta blockers, may cause deterioration. Deterioration is usually due to undertreatment, but may also be a result of excessive acetylcholinesterase inhibitor medication (a cholinergic crisis), and it may be difficult to distinguish these two situations.

A specific complication is neonatal myasthenia, where the new born baby receives the acetylcholine receptor antibodies from a mother with myasthenia gravis. The neonatal symptoms may take several days to develop, and require careful observation.

What are the evidence based management approaches?

There are national UK (Norwood 2014; Sussman 2015) and international (Elsais 2014; Sanders 2016, Gronseth 2020) guidelines on the management of myasthenia gravis. Management will usually be initiated by the neurologist, but as a chronic condition the general practitioner will be involved in the long term management and monitoring, usually with the patient continuing with neurological follow up. The general practitioner may also be the first point of contact for an acute deterioration.

First line treatment is with pyridostigmine. This is an acetylcholinesterase inhibitor. This prevents the breakdown of the neuromuscular transmitter acetylcholine at the neuromuscular transmission, facilitating neuromuscular transmission. Dosage depends on the severity of symptoms, but initially may be commenced at 30-60 mg four times daily. The tablets are 60mg and may be split in two. The half life is short, and the effect of a single table is only a few hours. The cholinergic side effects may include abdominal cramps and diarrhoea. Propantheline or mebeverine may help with these side effects. The dose of pyridostigmine will need to be adjusted according to patient response, and is very variable between patients. The dose is initially titrated to the lowest effective dose. Individual patients may learn to adjust their medication according to response, and activity.

Pyridostigmine is a symptomatic treatment, and does not treat the underlying cause of the autoimmune condition (usually antibodies to the acetylcholine receptor). The next step in management would be with an immunosuppressant,

usually prednisolone. In order to minimise the side effects of long term steroids, a steroid sparing agent such as azathioprine may be introduced (Palace 1998). The activity of the enzyme thiopurine S-methyltransferase (TPMT) may be reduced in some people. TPMT is involved in the metabolism of azathioprine, and patients with a reduced activity level are at higher risk of severe myelosuppression by the azathioprine. TPMT activity level is measured as a blood test before commencing azathioprine, as a lower dose may be needed. Other possible immunosuppressants include cyclosporine, mycophenolate, and methotrexate,. Medication to prevent steroid induced osteoporosis is an important consideration, usually with reference to local guidelines. Azathioprine requires regular long term monitoring of full blood count (in particular white cell count) and increasingly there will be local guidelines on shared care for monitoring and prescribing. Prednisolone may induce or exacerbate diabetes. It is important to be aware that commencement of corticosteroid treatment may cause an initial deterioration in the myasthenia symptoms.

The majority of patients may be managed on this regime, but some patients require additional treatment, including intravenous immunoglobulin or plasma exchange for acute deterioration. Newer developments include more aggressive immunosuppression with drugs such as rituximab, and this would be directed by an expert in myasthenia gravis (Dalakas 2020). As a rare disease it is difficult to perform randomized clinical trials, but there is an increasing body of evidence. It may be difficult to generalise the results of these trials to individual patients. There is clinical trial evidence to indicate that thymectomy in non-thymomatous myasthenia gravis may be helpful in long term management of selected patients

with myasthenia gravis (Wolfe 2019), and this may be using a thoracotomy or endoscopic approach. Thymectomy is indicated in patients with myasthenia gravis and thymoma (primarily to remove the tumour and may not improve the myasthenia gravis). (Gronseth 2020)

In patients with persistent disability related to muscle weakness, physiotherapy and other rehabilitation approaches are indicated. It is usually necessary to continue immunosuppression for many years, but with attempts at reduction where possible. There may be remission, and recurrence of myasthenia gravis.

Planning for pregnancy should be made, to optimise myasthenic treatment and minimize risk to the foetus (Norwood 2014)]. The majority of women remain stable during pregnancy, and any worsening is more likely in the first few months after delivery. The aim is for spontaneous vaginal delivery, but it is important that the baby has rapid access to neonatal intensive care if needed.

Conclusion

Myasthenia Gravis is a rare autoimmune disorder affecting neuromuscular junction function. In its most frequent presentation it should be considered, and provisionally diagnosable, by the general practitioner on the basis of clinical history of fatiguing muscle weakness, and basic clinical examination. Further initial diagnosis and management should be by referral to a neurologist.

Myasthenia gravis is a chronic condition, and over the years there will be monitoring and adjustment of treatment. Monitoring of the potential rare complications of immunosuppressant treatment is important. Most important is

the recognition of impending myasthenic crisis (for which there should be a low threshold for hospital admission), and for myasthenic crisis for which urgent hospital admission to an intensive care unit is essential, to minimise preventable mortality from the condition.

REFERENCES

Alshekhlee A, Miles JD, Katirji B, Preston DC, Kaminski HJ. Incidence and mortality rates of myasthenia gravis and myasthenic crisis in US Hospital. *Neurology* 2009;72:1548-54.

Dalakas MC. Progress in the therapy of myasthenia gravis: getting closer to effective targeted immunotherapies. *Current Opinion in Neurology* 2020 (online ahead of print)

Elsais A, Argove Z, Evoli A, et al. EFNS/ENS guidelines for the treatment of ocular myasthenia. *European Journal of Neurology* 2014;21:687-693.

Gronseth GS, Barohn R, Narayanaswami P. Practice advisory: thymectomy for myasthenia gravis (practice parameter update). Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2020;94:705-709.

Norwood F, Dhanjal M, Hill M. et al. Myasthenia in pregnancy: best practice guidelines from a UK multispecialty working group. *Journal of Neurology, Neurosurgery & Psychiatry* 2014;85:538-543.

Palace J, Newsom Davis J, Lecky B. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. *Myasthenia Gravis Study Group. Neurology* 1998;50:1778-1783.

Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: Executive summary. *Neurology*. 2016;87:419-425.

Sussman J, Farrugia ME, Maddison P, Hill M, Leite MI, Hilton-Jones D. Myasthenia gravis: Association of British Neurologists' management guidelines. *Practical Neurology* 2015;15:199-206.

Vincent A. *Neuroscience* 2020;439:48-61. Antibodies and receptors: from neuromuscular junction to central nervous system.

Wolfe GJ, Kaminski HJ, Aban IB, Minisman G, Kuo HC, Marx A.. Long-term effect of thymectomy plus prednisone alone in patients with non-thymomatous myasthenia gravis: 2-year extension of the MGTX randomised trial. *Lancet Neurology* 2019;18:259-268.

Additional information

Further information and patient support is available from:

Muscular Dystrophy UK. www.musculardystrophyuk.org

Myaware. www.myaware.org

Figures and tables