Myasthenia Gravis (MG)

Description

Described by Thomas Willis in 1672, it is an acquired autoimmune disease with antibodies against the nicotinic ACh receptor at the NMJ or muscle-specific tyrosine kinase (MuSK). This → muscular weakness with easy fatiguability, worse on exercise and improves with rest.

Epidemiology

- Incidence of ~3/100,000, prevalence of 15-20/100,000
- Mean age at onset for women is 34.9 years and for men it is 48.5 years.
- Peak incidence is in the third decade for women and sixth or seventh decade in men.

Aetiology

- About 10% with MG have a thymoma and ~50% with thymoma also have MG.
- Can be familial. Autoimmune disease associations. Most cases are however idiopathic.
- Can be aggravated by or induced by drugs e.g. antibiotics, CVS drugs GA, and others

Presentation

50% present with ocular muscles problems and 90% experience them at some stage.
Weakness variable but usually exposed with repeated/extended testing as fatiguable.

- Ptosis typical (pat tilt head up to compensate) with diplopia from weakness of eye mm.
- Weakness more marked in proximal muscles. Isolated weakness of a limb is uncommon.
- Weakness of the following muscles may also be seen:
    - Small muscles of the hands (finger extensors).
    - Deltoid and triceps muscles.
    - Bulbar muscles - common; causing a nasal sound to speech that is slurred.
    - Facial muscles - very common, producing an abnormal horizontal smile with a furrowed brow that compensates for ptosis.
    - Muscles of mastication - thus eating difficult and may be jaw drop.
    - Flexors and extensors of the head - are often weak.
- Symmetrical weakness of a number of other muscles may produce difficulty with walking, sitting or even holding the head up.
- Seizures may occur and there is a case report of undiagnosed myasthenia gravis mistakenly thought to be eclampsia.
- **NB. There is no muscle wasting or fasciculation. Tone is normal. Sensation is unimpaired and tendon reflexes are normal.**

Progression

- The most typical pattern is for progressive disease over weeks to months although sometimes the disease can remain mild & just ocular for years.
- Disease is confined to the ocular muscles in only around 15%.
- ~90% develop general disease within a year, time to max. weakness is <36yrs in >80%.
- In severe and general weakness it is rare for the ocular muscles to be unaffected.
- Intercurrent illness, medications, pregnancy, emotions and hypoK^+ can all exacerbate weakness and may precipitate a myasthenic crisis and respiratory inadequacy.
- Spontaneous remissions are rare. Full and prolonged remissions are even rarer. Most remissions from treatment occur in the first 3 years of the disease.
- Choking, drooling and difficulty with chewing or swallowing can → aspiration pneumonia.

Potentially dangerous drugs

Antibiotics: aminoglycosides, ciprofloxacin, macrolides, tetracycline, ampicillin, clindamycin
Beta blockers: propranolol, atenolol, timolol eyedrops
Calcium channel blockers: e.g. verapamil
Class I anti-arrhthymics: Procainamide, quinidine
Local anaesthetics: Lignocaine, prilocaine
Neuromuscular blocking agents: atracurium, suxamethonium
Anticonvulsants: phenytoin, phenobarbitone, paraldehyde, $MgSO_4$
Psychotropics: Li, chlorpromazine, amitriptyline, droperidol, haloperidol
Other: D-penicillamine, opiates, chloroquine, high dose steroids

Differential diagnosis

Causes of generalised muscle weakness: MS, MNS, ME, hyperthyroidism, myopathies, Guillain-Bare, Eaton-Lambert syndrome, toxins e.g. botulin, organophosphate poisoning.
Causes of ocular symptoms: Horner's syndrome, Oculopharyngeal muscular dystrophy.
Bulbar symptoms: Amyotrophic lateral sclerosis/motor neurone disease.

Investigations

Antibodies:

- ACh-receptor antibodies (Positive in 50-85%. False pos with Lambert-Eaton syndrome, thymoma, small cell lung cancer, penicillamine and elderly.)
- Anti-striated muscle antibody (anti-SM Ab) (risk of thymoma if <40yrs)
- Anti-MuSK antibodies - may be present in up to a third of patients.

TFTs
Imaging: CT or MRI are used to gain images of the thymus & lungs (?cancer)
EMG: Repetitive stimulation may show early fatigue and failure to respond.
The Tensilon® test:

- **Edrophonium** (short-acting anticholinesterase) 1mg IV first (to check that weakness not due to cholinergic crisis from excess anticholinesterase) then rest of 10mg dose.
- **SE:** excessive vagal tone → marked bradycardia so have atropine at hand.
- A positive test is substantial improvement in muscle power but drug lasts only 1-5min.

Spirometry: if FVC approaching ≤15ml/kg consider intubation.

Management

- Close monitoring is required, patients can deteriorate rapidly.

Crisis Resus:

- Intubate (rocuronium preferred, avoid sux) for resp failure. Consider NIV if pCO_2 ok.
- High quality ventilator care is needed, excess secretions and VAP are potential Cx

Specific:

- Crisis Mx:
    - Anticholinesterases controversial in a crisis (some suggest temp withdrawal). If given, **pyridostigmine** 2-3mg IV or **neostigmine** 0.5mg IV/IM/SC. **SE:** GIT.
    - Plasmapheresis or IVIG (but may take a few days to be beneficial)
    - Immunomodulators: **steroids**, **azathioprine**, **cyclosporin** or **mycophenolate mofetil** (but may take days/wks to be beneficial)
- Outpatient Mx: anticholinesterases e.g. **pyridostigmine** 60-90mg q4h PO.
- Thymectomy often beneficial especially if thymoma.

Supportive

- Avoid pyrexia, maintain electrolyte balance. Modified diet if swallowing problems.

Complications

- Aspiration pneumonia due to throat muscle weakness.
- Acute respiratory failure during an exacerbation.
- Neonates may be symptomatic from Ab crossing placenta or arthrogryposis multiplex.

Prognosis

- A typical picture involves exacerbations and remissions.
- Without treatment there is a mortality of 25 to 30% but with modern management of crises this falls to about 4%.
- Most of the mortality occurs in the first 3 years or so, and it tends not to worsen.
- Onset after 40 years old, a rapid and progressive disease and thymoma are all bad prognostic signs.
- Intercurrent infection and hot weather can aggravate features.

Seronegative MG

- There is evidence to suggest that a subgroup of MG patients exist who are seronegative to the usual tests but have muscle specific tyrosine kinase (MuSK) autoantibodies (in up to 40%).
- Predominantly female<40yrs: a third fail to respond to anticholinesterase drugs but ~50% respond to immunosuppression with steroids.

Myasthenic syndrome

- Causes include:
    - Eaton-Lambert syndrome - associated with smoking & small cell lung cancer; may occur many years before detectable lesion
    - Autoimmune disorders
- Underlying aetiology is antibodies directed towards pre-synaptic calcium channels.
- Tends not to affect the eyes but proximal muscles of limbs.
- Repeated contraction of muscles can actually increase muscle strength.
- Autonomic dysfunction and hyporeflexia are also seen.
- No or little response in the Tensilon® test.
- Management includes **3,4-diaminopyridine** which increases the release of ACh from pre-synaptic nerve endings. IVIG may be helpful.
- Immunosuppression has been used but there is debate over its usefulness.
- Treatment of underlying cause can lead to much improvement.