Part II – Neurological Disorders

CHAPTER 13
MYOPATHIES AND MYASTHENIA GRAVIS

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CONTENTS

CHAPTER 13

MYOPATHIES AND MYASTHENIA GRAVIS

Myopathies are classified as either inherited or acquired. The main inherited myopathies are muscular dystrophies and acquired myopathies are inflammatory and non inflammatory. The main disorder which affects the neuromuscular junction is myasthenia gravis (MG). The aim of this chapter is to review the clinical features and management of muscular dystrophy, polymyositis and MG. The student should aim to be able to recognize these main muscle disorders and manage a patient presenting with muscle weakness.

Clinical history

The defining symptom of disorders of muscle and neuromuscular junction is weakness. Muscle weakness in myopathy is usually proximal. Patients typically present with weakness or difficulty elevating their arms above the shoulders, getting out of chairs or rising from the lying position. Other symptoms may include muscle pain and tenderness, muscle cramps on exercise and dysphagia. The history should include age of onset, time course, pattern and distribution of weakness, fatigability and any relevant past, family and drug history. Muscular dystrophies tend to have their onset in childhood or teens and are usually recognizable clinically. Inflammatory myopathies present with proximal muscle weakness, frequently with muscle pain, tenderness and sometimes dysphagia. The diagnostic characteristic of myasthenia gravis is fatigable muscle weakness, worse after exercise and commonly affecting the extra ocular and bulbar muscles.

Physical Examination

The characteristic clinical finding in myopathies and MG is muscle weakness. The weakness affects mainly the trunk and proximal limb muscles, and may also affect the neck muscles and facial expression. Power distally may be maintained in early disease but is lost or decreased later on. Muscle wasting occurs in most myopathies, tone is typically decreased and reflexes are preserved but may be reduced or absent in advanced disease. There are no sensory signs. Patients with muscle disease often have a very characteristic myopathic or "waddling" gait due to hip girdle weakness. The pattern of muscle weakness may indicate the underlying disorder. Muscle hypertrophy confined to the calves in boys is diagnostic of dystrophy and contractures may occur in long standing disease. Weakness of the eye muscles suggests myasthenia gravis whereas weakness of the face muscles is more of a feature of facioscapulohumeral dystrophy and myotonic dystrophy. Weakness of the neck muscles is typical of myasthenia gravis and polymyositis. Proximal weakness in combination with a skin rash is characteristic of dermatomyositis.

Key features of myopathy/MG

- proximal weakness
- fatigability
- hypertrophy
- contractures
- myopathic gait

Investigations

Routine bloods tests should include FBC, ESR, HIV, glucose, creatinine, electrolytes, thyroid function tests and serum creatine kinase (CK). CK is the best indicator of muscle disease with very high levels in inflammatory muscle disease and in most dystrophies but can be normal in myotonic dystrophy (MD) and facioscapulohumeral dystrophy (FSHD). It is important to remember that CK may be modestly elevated after strenuous exercise, injections, and viral infections and occasionally in healthy African populations which may sometimes lead to unnecessary investigation. Molecular genetic testing is increasingly important in the diagnosis of inherited muscle disease. An ECG and echocardiogram are indicated in the dystrophies to screen for cardiomyopathy

Electromyography (EMG)

This measures the electrical activity in a motor unit. In myopathies there is a decrease in the duration and amplitude of motor unit potentials with spontaneous fibrillations. There are also characteristic EMG findings in MG and in myotonic dystrophy.

Muscle biopsy

The biopsy site should be from moderately affected muscle and away from injection sites. This may show evidence of inflammation and dystrophic changes. Immunostaining is also helpful depending on the diagnosis.

Key points

- muscle disorders may be inherited (dystrophies) or acquired (polymyositis)
- proximal weakness is the key clinical finding in muscle disorders
- pattern of weakness points to the underlying disease
- marked elevation in CK is the best lab indicator of muscle disease

INHERITED MYOPATHIES

The main inherited myopathies are the dystrophies, myotonic dystrophy (MD), Duchenne (DMD), Becker (BMD), limb girdle (LGMD) and facioscapulohumeral (FSHD). The main clinical features and genetics are presented below (Table 13.1). DMD and BMD are both X-linked inherited and occur almost exclusively in males. Disease is caused by mutations of the X-linked dystrophin gene which leads to the complete absence of the muscle protein dystrophin in DMD or abnormal dystrophin in BMD. This affects both skeletal and cardiac muscle. The diagnosis of muscular dystrophy is usually based on clinical findings and a markedly elevated CK. A muscle biopsy can confirm the clinical diagnosis and genetic studies identify the causative mutation. Management includes genetic counselling.

Table 13.1 Characteristics of Muscular Dystrophies

Type	Genetics	Sex/age of onset	Clinical features
Myotonic	autosomal dominant	m = f,/birth to adult	proximal & distal limb weakness, facial weakness, myotonia, frontal balding, cataracts DM, cardiomyopathy
Duchenne	X-linked recessive	males/early childhood	proximal limb weakness, Gower's sign, calf pseudohypertrophy, cardiomyopathy
Becker	X-linked recessive	males/in teens or as adult	proximal limb weakness, slow progression, calf pseudohypertrophy, cramps, cardiomyopathy
Facioscapulo-humeral	autosomal dominant	m = f/in teens	facial weakness, winging of scapulae, proximal upper limb weakness, waddling gait, lumbar lordosis
Limb girdle	autosomal recessive autosomal dominant	m = f/in teens/young adult	proximal limb girdle weakness, cardiomyopathy (variable)

MYOTONIC DYSTROPHY

Myotonic dystrophy is an autosomal dominant multisystem disorder characterized by progressive proximal and distal muscle weakness, especially affecting the upper limbs. It gets its name from its characteristic of sustained muscle contraction or myotonia. It is the most common dystrophy with a prevalence of around 1/10,000 in high income countries. The frequency in Africa is not known and although isolated cases have been reported it is considered to be very uncommon in black populations there. It presents most commonly in adults of either sex but can present at any age.

Genetics

It is caused by an unstable expanded trinucleotide repeat (>50 CTG repeats) in the myotonin gene on chromosome 19q. There is a strong correlation between the number of repeats and the age of onset and thus severity of the disorder.

Clinical features

The clinical presentation varies from lethal disease at birth (congenital DM with CTG repeats above 1000) to very mild disease with late onset cataracts (CTG repeats 50-80). The classical or adult form (20-50 yrs; CTG repeats 200-500) presents with myotonia, frontal balding (even in women), bilateral ptosis, facial weakness, wasting and weakness of sternomastoids, proximal and distal weakness of mainly the upper limbs, cataracts, testicular atrophy, diabetes and sometimes cognitive impairment. Myotonia is persistence of muscle contraction, lasting several seconds if the muscle is actively used. It typically occurs during gripping or hand shaking when the affected person is unable to let go for the first few seconds. It is more pronounced during cold weather. Tapping affected muscles repeatedly with a tendon hammer demonstrates

a sustained dimple and a typical muscle contraction. Classic myotonic discharges on EMG testing sounding like a dive bomber are diagnostic. The diagnosis can be confirmed by DNA testing.

Management

Management includes genetic counselling especially as the severe congenital form occurs in children of affected females with >100 repeats. Myotonia if disabling may be treated with phenytoin and also mexilitine if ECG QT interval is normal. There is an increased risk of sudden death and anaesthetic complications.

Key points

- MD is an autosomal dominant disorder confirmed by DNA testing
- uncommon in the black population in Africa
- C/Fs: ptosis, facial, sternomastoid &, limb weakness, cataracts, balding and DM
- characterised by sustained muscle contraction & inability to release grip
- increased risk of sudden death & anaesthetic complications
- management includes genetic counselling

DUCHENNE'S MUSCULAR DYSTROPHY

The incidence of DMD in high income countries is about 1 per 3,500 live births. There are few reports of DMD from Africa for comparison but a much lower prevalence of 1/250,000 was reported in one study in South Africa, suggesting that it is much more uncommon there.

Clinical features

DMD almost always presents in early childhood (1-5 yrs) usually presenting early with difficulty or a delay in walking and a characteristic toe walking gait. Other diagnostic features are calf hypertrophy and contractures. Patients may also demonstrate "Gower's sign" which is using the hands to climb up the legs whilst getting up from the squatting or lying position (Fig 13.2). The main complications are scoliosis, cardiomyopathy and immobility with nearly all patients becoming wheelchair bound by the end of the first decade. There is no long term effective drug treatment although the use of steroids is now established practice in some high income countries.

Prognosis

In high income countries most deaths used to occur before or in the early teenage years but now occur in late teens or early twenties. This improved survival is mainly due to intervention with assisted nocturnal ventilation and early management of complications.

BECKER'S MUSCULAR DYSTROPHY

The incidence of BMD in high income countries is around 1/35-40,000. There are few reports from Africa but a very much lower prevalence of <1/750,000 has been reported from South Africa. The range of symptoms is similar to DMD but it is much milder. It frequently has its onset during the first decades at around 10-11 years of age but many are mild and usually go unnoticed in childhood. They present mostly in teens or early adult life with mild limb girdle

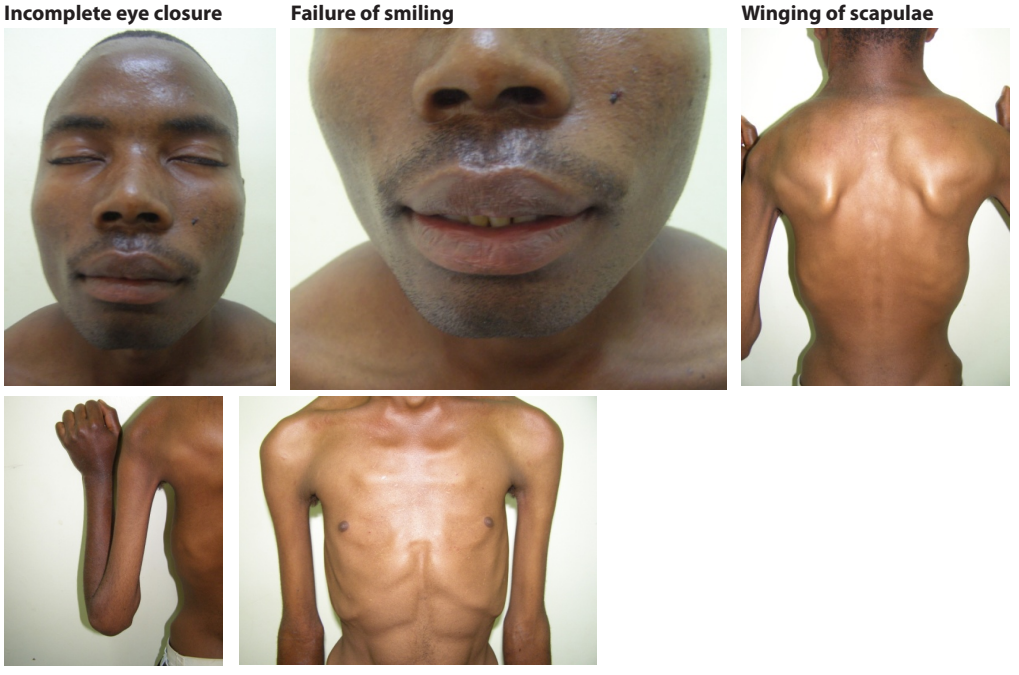
weakness, cramps and calf hypertrophy. Many are wheelchair bound by their late 20s. Cardiac involvement occurs in around 10% and shortens life expectancy.

Key points

- Duchenne presents with walking difficulties in boys in very early childhood
- most progress to wheelchair dependence by the start of second decade
- death usually occurs before or by early teens in Duchenne in Africa
- Becker is a much milder form affecting males in their early teens
- C/Fs: calf hypertrophy, contractures and Gower manoeuvre
- elevation of CK is a characteristic finding in all dystrophies

OTHER DYSTROPHIES

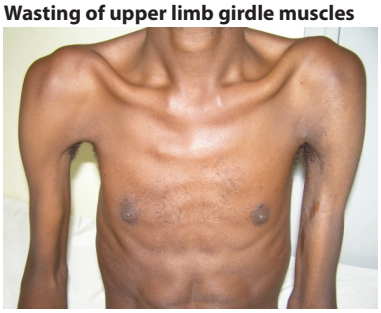
The other main muscular dystrophies include facioscapulohumeral dystrophy (FSHD)(Fig. 13.1), an autosomal dominant dystrophy caused by a complex genetic defect on chromosome 4q and limb girdle muscular dystrophy (LGMD)(Fig. 13.2). LGMD is genetically very heterogeneous: mostly autosomal recessive with at least 15 genes involved and less frequently autosomal dominant with at least 8 genes involved. These dystrophies are uncommon with a reported incidence rate for FSHD in high income countries of 1-2/100,000. Their frequency in Africa is not known. The pattern of muscle weakness follows the description in their names. Severity is variable from the uncommon rapidly fatal mainly childhood forms, to the more common mild and slowly progressive mainly adult forms.

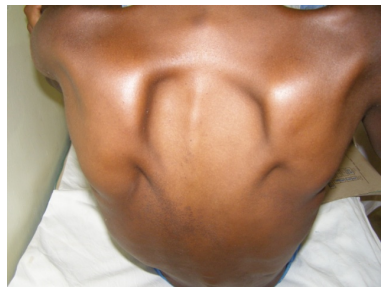


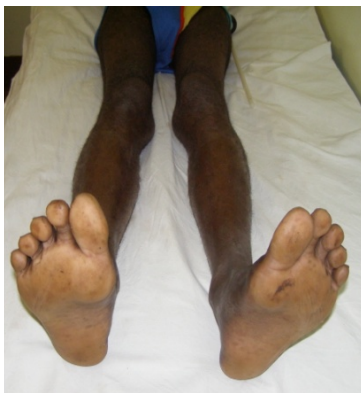
Wasting of proximal (humeral) limb muscles, triceps & biceps

Figure 13. 1 Facioscapulohumeral dystrophy

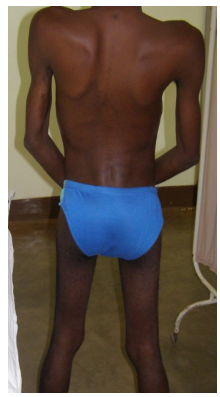
Wasting of upper limb girdle muscles

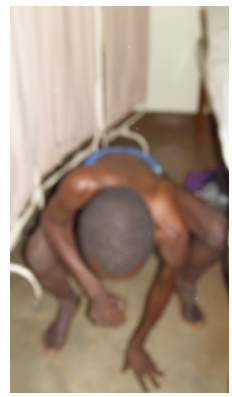






Wasting of proximal lower limb girdle muscles





Gower's manoeuvre

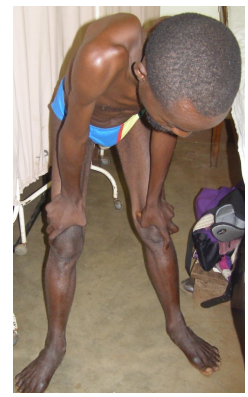


Figure 13. 2 Limb girdle muscular dystrophy

Key points

- muscular dystrophies are uncommon in adults
- two main types, limb girdle and facioscapulohumeral
- the pattern of muscle weakness follows their name
- survival into early and mid adulthood is a feature of both types

INFLAMMATORY MYOPATHIES

DERMATOMYOSITIS AND POLYMYOSITIS

Dermatomyositis and polymyositis are the main inflammatory myopathies. They are defined by inflammation in muscles and their general characteristics are presented below (Table 13.2). Their approximate frequency in high income countries is 5/100,000. In Africa they mostly affect the age group 20-40 yrs but occur in other age groups. Females are more commonly affected than males.

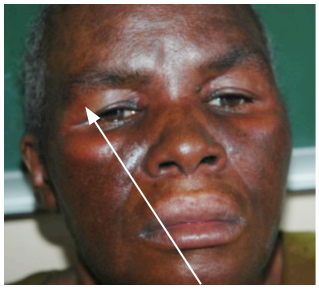
Clinical features

Patients present with sub acute mainly proximal muscle weakness and pain over months but occasionally over weeks. Dysphagia may occur because of involvement of pharyngeal muscles.

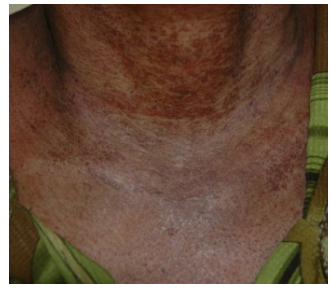
In dermatomyositis both skin and muscle are involved. On examination, there is marked symmetrical proximal weakness and signs of muscle atrophy in long standing disease. There is a characteristic blue-purple rash, plus oedema of upper eye lids (heliotrope), erythema over cheeks, knuckles and chest (Fig. 13.3) and dilated capillaries at the base of finger nails.

Table 13.2 Characteristics of inflammatory myopathies

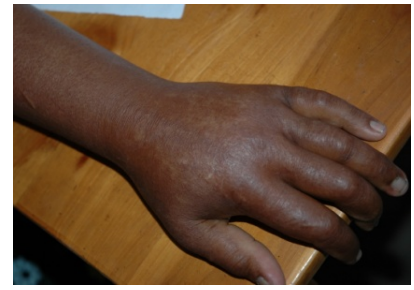
Characteristics	Polymyositis	Dermatomyositis
age group	20-40 yrs	10-50 yrs
female:male ratio	2:1	2:1
onset	months	weeks to months
proximal muscle weakness	yes	yes
skin involvement	no	yes
malignancy	no	slight risk
elevation in ESR & CK	marked	marked
response to steroids	yes	yes



Rash/oedema/heliotrope sign



Rash on neck & chest



Rash/oedema over hands/knuckles

Figure 13. 3 Dermatomyositis

Investigations

The ESR and serum CK are markedly elevated in polymyositis. The diagnosis is confirmed by muscle biopsy. Malignancy should be screened for in patients with dermatomyositis.

Management

The management of polymyositis is based on corticosteroids and immunosuppressant drugs. Treatment is with prednisolone 1mg/kg or 60 mg/po/daily. After months, when CK returns to normal and there is clinical improvement, the steroids can be reduced gradually by 5 mg decrements per dose on the alternate day, until the steroids are being administered only on alternate days. If the improvement is maintained, the prednisolone can be further decreased by 10 mg decrements every 4 weeks, until a maintenance dose is found. The usual maintenance dose is 5-10 mg prednisolone on alternate days. This may need to be continued for a further period of 3-6 months. Consider using an immunosuppressant drug from the start with steroids. The drug of choice is azathioprine 2.5 mg/kg/day. Start with 50 mg per day and increase by weekly intervals to 125-150 mg daily in divided doses. The main side effects are bone marrow suppression and hepatic toxicity. A FBC and liver function should be checked at the start and at least every four months during treatment with azathioprine. Alternatives are methotrexate or cyclophosphamide.

Key points

- C/Fs include progressive proximal muscle weakness & pain over weeks/months
- proximal weakness & characteristic skin rash are diagnostic of dermatomyositis
- ESR and CK are both elevated
- diagnosis is confirmed by muscle biopsy
- treatment is with steroids & another immunosuppressant for >6-12 months

INCLUSION BODY MYOSITIS

Inclusion body myositis (IBM) is another form of progressive inflammatory muscle disease which occurs in people >50 yrs. It is relatively common in high income countries but its frequency in Africa is not known. It occurs more frequently in older males and presents with painless proximal weakness with selective involvement of finger flexors and quadriceps muscles and frequently involves swallowing. Diagnosis is established by muscle biopsy and long term treatment is unsatisfactory. The differential diagnosis of inflammatory myopathies includes myasthenia gravis, non inflammatory myopathies and neuropathies.

OTHER MYOPATHIES

There is a large group of acquired non inflammatory myopathies. The main causes are outlined in table 13.3. Patients may range from being relatively asymptomatic with just muscle wasting to having severe weakness of limbs and trunk muscles. Most cases remit once the underlying disorder is treated or the offending drug is withdrawn.

Table 13.3 Causes of acquired non inflammatory myopathies

Classification	Causes
infections	HIV, TB
endocrine	thyroid disorders Cushing's disease
neoplastic	any malignancy
metabolic	hyper/hypokalaemia
organ failure	chronic cardiac, respiratory, liver disease
drugs	alcohol, steroids, statins, ARTs (zidovudine)

MYASTHENIA GRAVIS

Myasthenia gravis (MG) is an uncommon autoimmune disease that is caused by acetylcholine receptor antibodies (AChRA) at the neuromuscular junction. The antibody binds to the post synaptic acetylcholine receptor sites which makes them unavailable for the transmission of nerve impulses. It is a worldwide disorder with an incidence in high income countries of around 3-30/1,000,000 per year and with most cases expected to survive, the approximate prevalence rate is much higher at around 10/100,000 with a reported increase over time in age related MG. The incidence rates across Africa are not known, but a detailed study from Cape Town in SA using AChRAs as in indicator of MG reported an incidence rate there of 12.6/1,000,000 which is similar to that in high income countries. MG affects all age groups but mainly females in the age group 20-40 yrs and males in an older age group. It is associated with hyperplasia of the thymus (70%) and less commonly with thymoma (10%).

Clinical features

Symptoms

The most important diagnostic feature of MG is fatigable muscle weakness. In the early stages, weakness may be transient and variable. The busiest muscles at rest are the ones most commonly affected and patients frequently present for the first time with involvement of the extra ocular muscles (diplopia), eyelid (ptosis) and bulbar muscles (dysphagia) (Fig. 13.4). These may be accompanied by proximal weakness of the limbs and involvement of the face, neck, and trunk; typically the weakness worsens after exercise or at the end of the day.

Signs

On examination, fatigable ptosis, diplopia and limitation of eye movement are the main demonstrable eye signs. Bulbar involvement is evident by nasal type speech, difficulty in swallowing and nasal regurgitation of liquids. Facial weakness is demonstrated by bilateral weakness of eye closure and inability to smile normally giving the characteristic "myasthenic snarl" (Fig. 13.4). Fatigability may be demonstrated by asking the patient to look upwards holding the gaze in that position for 1-2 mins or to repeatedly elevate the arms above the head (>20 times) in quick succession without resting. In patients with MG, ptosis or upper limb weakness may appear for the first time or becomes more obvious during these manoeuvres. Reflexes and sensory exam are normal. In about one fifth of cases, the weakness is confined to the eyes only. When this persists without systemic involvement, it is called ocular myasthenia gravis.

Differential diagnosis

The differential diagnosis includes other causes of neuromuscular weakness in Africa, including inflammatory myopathies, motor neurone disease, and other myopathies.

Complications

Involvement of bulbar and respiratory muscles in MG is a neurological emergency (Fig 13.4). The major complication is respiratory failure. It is essential to monitor patients closely who are weak or bedbound and to measure vital capacity regularly. A forced vital capacity level <1.5 litres requires ITU care and urgent assessment for emergency ventilation.

Table 13.4 Symptoms of weakness in myasthenia gravis

eyes	double vision & drooping eye lids
face, mouth	weakness smiling, chewing & swallowing
speech	voice weak & easily tires
limbs	weakness combing hair weak hand grip difficulty arising from chairs or climbing stairs
central muscles	head drop weakness sitting up
respiratory	shortness of breath

Figure 13.4 Myasthenia gravis

Key points

- key feature of MG is fatigable muscle weakness
- CFs are double vision, ptosis, dysphagia & weakness
- bulbar & respiratory involvement is an emergency
- may require ITU care & possible ventilation

Diagnosis

The diagnosis can be confirmed by a Tensilon (Edrophonium) test (Table 13.5). Edrophonium is a quick acting cholinesterase inhibitor which prevents available acetylcholine being broken down at the neuromuscular junction; this allows the excess acetylcholine to increase neuromuscular transmission and temporarily improve symptoms and signs. In order to carry out the test, two observers should ideally be present and cardiac resuscitation measures should be available. Other investigations are acetylcholine receptor antibodies (AChRA) which are present in 85% of patients with systemic MG. EMG shows a characteristic diagnostic pattern of decreasing amplitude of the compound muscle action potential with repeated stimulation. A CT of chest may show an enlarged thymus or a thymoma.

Table 13.5 Tensilon (edrophonium) test

1. tensilon 10 mg is drawn up into a syringe
2. a test dose of 3 mg is given intravenously as a bolus
3. observe the patient for any improvement in the weakness
4. in MG the weakness improves within a minute and lasts only 5 minutes or less
5. if there is no response then 7 mg is given intravenously
6. the outcome may be difficult to interpret hence the need for a second observer
7. atropine 0.5 to 1.0 mg should always be available for emergency iv use because of potential bradycardia.
8. atropine may also be given prophylactically just before the tensilon is given

Key points

- confirmatory tests are positive tensilon test, AChRA & EMG
- clinical diagnosis is confirmed by response to anticholinesterase drug treatment
- chest X-ray/CT may show thymic enlargement or infrequently a tumour

Management

The management of myasthenia involves the use of cholinesterase inhibitors and immunosuppression (Table 13.6). Treatment is very effective at reducing or abolishing weakness but requires scrupulous attention to detail.

Cholinesterase inhibitors

Pyridostigmine (60 mg tablets) is a long acting anticholinesterase which acts within 1 hour and lasts for 4 hours. The starting dose is 15 mg/po/qds and this is doubled every 2 days until the patient is taking 60 mg/po/qds. The patient's response will determine the dosage needed and the maximum total daily dose is 360 mg. Overdose causes a cholinergic crisis with severe bulbar and respiratory weakness, and patients need to be strictly warned about this possibility. The main side effects are abdominal pain and diarrhoea. Probanthaline 15-30 mg given 15 to 30 minutes before each dose of pyridostigmine is helpful to stop these in particular during the first few weeks of treatment. While anticholinesterases may suppress the symptoms they do not alter the disease and hence the need for immunosuppression.

Immunosuppression

Alternate day steroids are the treatment of choice. These are indicated in most cases. The patient should be admitted to hospital and started on prednisolone 10 mg/po/alternate days increasing slowly by 10 mg increments per dose (every second day) until 1.5 mg/kg or 100 mg is reached whichever is the lower dose. This should be maintained until the patient is stable in remission. Improvement begins after 2-4 weeks and maximises at 6-12 months. Then prednisolone is reduced by 10 mg every 4 weeks until the patient is on 40 mg alternate days, and by 5 mg every 4 weeks until on 20 mg and then by 1 mg every month thereafter. If during this steroid reduction stage there is a relapse, then begin again as at the start of treatment. If there is steroid intolerance or lack of response, azathioprine is started in addition to steroids at a dose of 25 mg/po/bd and increased by 25 mg/daily until the patient is on 2.5 mg/kg/po or 150 mg/po/daily. The main side effect is bone marrow depression. The patient needs a FBC and liver function tests every week for 2 months and then every 3 months.

Intravenous immunoglobulin (IVIG) or plasma exchange and ventilation

These may be needed in myasthenic crisis. The main indications for their use are increasing respiratory and bulbar weakness. However, these treatment options are unavailable at most centres in Africa. Respiratory failure (FVC <1.5 litres) is an urgent indication for consideration for mechanical ventilation.

Thymectomy

This is considered in patients on treatment who are under 45 years or who have the disease for less than 10 years or for suspected thymoma. As many as half the patients will go into complete remission after a thymectomy.

Table 13.6 Summary of management of myasthenia gravis

Treatment	Drugs	Indication
cholinesterase inhibitors	pyridostigmine	any muscle weakness
immunosuppression	prednisolone azathioprine	inadequate control on pyridostigmine alone inadequate control on prednisolone & pyridostigmine
IVIG/plasma exchange		myasthenic crisis, bulbar & respiratory weakness
ventilation		bulbar/respiratory failure
thymectomy		all patients <45 years and suspected thymoma at any age

Key points

- mainstay of management is with pyridostigmine and steroids
- steroids should be introduced slowly under close supervision
- IVIG and plasma exchange are indicated in myasthenic crisis
- ventilation is necessary in respiratory failure
- treatment of MG is very effective but requires scrupulous attention to detail

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