Myopathies

Myopathies are a heterogeneous group of conditions with diverse aetiologies. They usually affect muscle without involving the nervous system or any disorder of the neuromuscular junction.

The muscular dystrophies are the most common of such disorders and Duchenne muscular dystrophy is the most common muscular dystrophy. However, the broad range of myopathies is outlined in the boxes below which include some of the rare primary disorders of muscle as well as acquired myopathies.

The subsequent sections put these conditions in context and highlight some contrasting diagnostic and clinical features. Most of the congenital myopathies are chronic and slowly progressive. However, metabolic, inflammatory, toxic and endocrine myopathies present subacutely or even acutely and this requires awareness amongst front-line physicians to recognise and diagnose myopathy.

Aetiology

There are many causes of myopathy, both inherited and acquired.\(^1\)

**Inherited myopathies\(^2, 3, 4\)**

- Inherited biochemical defects causing myopathy - eg, mitochondrial myopathy, lipid storage disease (eg, carnitine palmitoyltransferase deficiency, myopathic carnitine deficiency), disorders of purine nucleotide metabolism, glycogen storage disorders (eg, Pompe's disease, McArdle's disease).\(^5\)

**Acquired myopathies**

- Immunologically mediated: eg, polymyositis, dermatomyositis, systemic lupus erythematosis, rheumatoid arthritis, polyarteritis nodosa, polymyalgia rheumatica, inclusion body myositis.
- Non inflammatory myopathies: eg, hyperthyroidism, hypothyroidism, Cushing's syndrome, diabetes mellitus, hyperparathyroidism, hyperparathyroidism, electrolyte disturbances (hypercalcaemia, hypokalaemia).
- Toxic and cachectic myopathies: eg, acute alcoholic myopathy with myoglobinuria, paraneoplastic myopathy, protein malnutrition, drugs (eg, steroids, statins, zidovudine, clofibrate, colchicine, cocaine).
- Infection: eg, trichinosis, toxoplasmosis, human immunodeficiency virus (HIV), Coxsackie viruses, influenza, Lyme disease.

Epidemiology

These are all relatively uncommon diseases:

- Duchenne muscular dystrophy is easily the most common childhood-onset muscular dystrophy and affects 1 in 3,300 boys.\(^6\) The prevalence of Duchenne muscular dystrophy is 63 cases per million.
- The prevalence of the Becker phenotype is 24 cases per million.
- Congenital muscular dystrophy is approximately 50% as common as Duchenne muscular dystrophy.
Clinical features of myopathy

- The hallmark symptom of myopathy (and neuromuscular disease) is weakness.
- Weakness predominantly affecting proximal muscle groups (shoulder and limb girdles) is typical.
- Weakness manifests itself in different ways at different ages:
  - Decreased fetal movements in utero.
  - Floppy infant neonatally.
  - Motor delay in the toddler years.
  - Reduced muscle strength and power in older children and adults.

- Myalgia may occur in inflammatory myopathies.
- Muscle-stretch reflexes are preserved.
- Somatosensory reflexes are preserved.
- Variation of strength with exercise (either increasing or decreasing) can occur:
  - Fluctuating muscle power suggests metabolic myopathy (for example, McArdle’s disease).
  - Fatigability (or progressive weakness with exertion, relieved by rest) is a feature of myasthenia gravis where the defect is in neuromuscular transmission.

History

- Common symptoms:
  - Malaise, fatigue.
  - Symmetrical proximal muscle weakness with absence of sensory symptoms (paraesthesia).
  - Atrophy of muscles (and reduced reflexes) occurs late with myopathies (early with neuropathy).
  - Waddling gait of Duchenne muscular dystrophy at age 3-6 years is typical.

- Acuteness of symptoms:
  - Weakness over hours suggests a toxic cause or episodic paralysis.
  - Weakness developing over days - consider dermatomyositis or rhabdomyolysis.
  - Weakness over weeks suggests polymyositis, steroid myopathy, endocrine myopathy.

- Affected muscle groups:
  - Proximal muscle groups - difficulty rising from chair, climbing stairs, shaving, hair combing.
  - Distal muscles - difficulty walking (flapping gait), grasping, handwriting.

- Metabolic myopathies present with:
  - Difficulty with exercise.
  - Cramps and myalgia with exercise (early with glycogen storage disorders and after prolonged exercise with lipid storage disorders).
  - Myoglobinuria.
  - Progressive muscle weakness in some metabolic myopathies.

- Past medical history, including autoimmune disease (eg, systemic lupus erythematosus, rheumatoid arthritis, polyarteritis nodosa), endocrine disease, kidney disease, alcoholism
- Family history of muscular dystrophy or any other relevant conditions or myopathies.
- Medication - eg, steroids, lipid-lowering drugs, colchicine, heroin, zidovudine.
- Occupational history - eg, pottery industry - glazing salts can cause hypokalaemic paralysis.

Examination

- Symmetrical proximal muscle weakness.
- Muscle tenderness is very rare with myopathy.
- Fever with inflammatory causes.
- There is usually no wasting but there may be hypertrophy of muscle (atrophy is a late sign).
- Reflexes and sensation are usually normal.
- Hypotonia is common in some myopathies (for example, congenital myopathies).
There may be helpful additional signs such as the skin changes of dermatomyositis.

Urine should be examined - myoglobinuria in acute alcoholic myopathy can cause renal tubular necrosis.

**Differential diagnosis**

This list includes other conditions causing weakness:

- Guillain-Barré syndrome.
- Lambert-Eaton myasthenic syndrome.
- Myasthenia gravis.
- Cerebral palsy.
- Spinal muscular atrophy.
- Congenital hypomyelinating neuropathies.

It may be difficult to distinguish myopathy from peripheral neuropathy. The distinguishing clinical features of peripheral neuropathy are:

- Weakness affecting distal muscles - although there are exceptions:
  - Myopathy where distal muscle groups are affected (myotonic dystrophy, myopathy of Welander).
  - Peripheral neuropathies which affect proximal muscles (diabetic amyotrophy, motor neurone disease).

- Reduced muscle - stretch reflexes.
- Fasciculations.
- Somatosensory abnormalities.

Some complex cases may have both neurogenic and myopathic disorders which can lead to diagnostic confusion:

- Diabetes mellitus can cause both neuropathy and inflammatory myopathy.
- Cancer can cause dermatomyositis and chemotherapy may cause peripheral neuropathy in the same patient.
- Radiculopathy (from degenerative disc disease) can occur in patients with myopathy.

**Investigations**

**Blood and urine tests**

These, together with ECG examination, are most useful in acute situations.

- Creatine kinase (with isoenzymes) - level may be 50-100 x normal reference range.
- Renal function and electrolytes including calcium and magnesium.
- FBC, ESR, TFTs, antinuclear antibodies.
- Serum myoglobin.
- Urinalysis and urine microscopy - myoglobinuria inferred by positive urinalysis with few red cells at microscopy.

**ECG**

May show:

- Changes of hypokalaemia - increased P-R interval, U waves, wide QRS and nonspecific ST-T changes.
- Sinus arrhythmias, deep Q waves and elevated R waves precordially (for example, in Duchenne muscular dystrophy).
Muscle biopsy
Muscle biopsy is important in diagnosis but findings under the microscope are rarely pathognomonic. Interpretation requires close consideration of the clinical history in conjunction with the microscopic features to make a diagnosis.

Electromyography
- Excludes primarily neurogenic processes (for example, spinal muscular atrophy).
- Proximal muscles of lower extremities often exhibit the most prominent features.
- Often helps to confirm diagnosis but is not in itself diagnostic.

Magnetic resonance imaging (MRI)
- May help to exclude neurological disease.
- May help in assessing complications (musculoskeletal or involving other organs).

Genetic testing
The genetic basis of the primary myopathies means that genetic testing can be essential to the specific diagnosis. As defects are identified, repair strategies have been developed. Many are now at the stage of clinical testing.\[7\]

Management
This depends on the diagnosis as well as the severity and extent of disease.

Emergency management
Myopathy can, rarely, present acutely or with acute complications. Examples include:

- Respiratory difficulties:
  - Respiratory failure can occur in a number of the myopathies.
  - Aspiration pneumonia may also occur.
  - Cardiac complications may be associated including cardiomyopathy and conduction defects.

- Some metabolic myopathies:
  - Hypokalaemia: oral supplements, cautious use of intravenous potassium, and prophylactic drugs (spironolactone and acetazolamide).
  - Hyperkalaemia: carbohydrate loading (for example, early in attacks with hyperkalaemic periodic paralysis), glucose and insulin.

- Polymyalgia rheumatica: treatment with corticosteroids. Be aware of associated giant cell arteritis.

Long-term care
- Myopathy associated with respiratory failure:
  - Monitor pulmonary function (early restrictive pattern may occur before onset of symptoms).
  - Beware of symptoms of nocturnal hypoxia (poor sleep, nightmares, headaches).
  - Physiotherapy.
  - May require tracheostomy and permanent ventilation.

- Specific medication: may be useful in particular situations for particular myopathies.
- Genetic counselling.
- Surgery (eg tendon release surgery): for example, to prolong the ability to walk.
- Physical aids: walking aids, wheelchairs, adaptive devices
- Family support.
- Dietary advice: both general (for example, to prevent obesity) and specific dietary advice may be required for the underlying cause of myopathy.

Complications
- Respiratory failure.
- Aspiration pneumonia.
- Musculoskeletal problems include joint contractures, chest deformities and spinal deformities, including scoliosis.
- Malignant hyperthermia can occur with central core disease.

Prognosis
This depends on the specific diagnosis. The primary disorders are incurable conditions with varied prognosis. Secondary myopathy may be corrected by treating the underlying cause.
Prevention

Genetic counselling is, in some of the most common myopathies such as Duchenne muscular dystrophy, the only intervention that can prevent disease. In general:

- Give genetic counselling early.
- Test early for carrier status where appropriate.
- Consider prenatal diagnostic testing where appropriate.
- Advances in molecular genetics may help in the future.

Further reading & references

- EFNS guideline on diagnosis and management of limb girdle muscular dystrophies; European Federation of Neurological Societies (2007)
- Fascioscapulohumeral muscular dystrophy 1A, FSHD1; Online Mendelian Inheritance in Man (OMIM)
- Facial Dystrophy, Duchenne Type, DMD; Online Mendelian Inheritance in Man (OMIM)

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