Limb-girdle Muscular Dystrophy

Description

The term limb-girdle muscular dystrophy (LGMD) refers to a group of rare, inherited disorders which predominantly affect the muscles around the shoulder girdle and hip girdle, causing progressive muscle weakness.\[^{1}\] Other muscles, including the heart, may be affected in some types of LGMD. The individual forms of LGMD vary widely in their genetics and clinical features.\[^{2}\]

There are over 30 subtypes of LGMD.\[^{3}\] LGMD includes 15 autosomal recessive subtypes and seven autosomal dominant subtypes. Autosomal recessive dystrophy is far more common than autosomal dominant dystrophy.\[^{4}\] See the table at the bottom for further details of the individual LGMD types.

Aetiology and classification\[^{2}\]

Several different aspects of muscle function seem to be involved.

Currently, LGMDs are classified into two main groups: autosomal dominant (group 1) or recessive (group 2). Within these groups, the subtypes are designated by letters (allocated in chronological order of gene identification).

The terminology of LGMDs may also relate to the protein involved in the pathology - eg, LGMDs 2C-F are termed sarcoglycanopathies. Other proteins involved include dystroglycan, fukutin-related protein, calpain, dysferlin and telethonin.\[^{5}\]

Epidemiology\[^{2}\]

- The LGMDs individually are rare, with some forms reported in only a few families.
- LGMD2A is the most frequent type of LGMD worldwide.\[^{6}\]
- The recessive forms are more common than the autosomal dominant forms.
- In the UK, LGMDs comprised 6.2% of the population of a specialist muscle clinic, giving a prevalence of 2.27/100,000.\[^{7}\]

Presentation\[^{2, 8}\]

By definition, all LGMDs involve the proximal muscles of the shoulder and pelvic girdles. However, the precise symptoms and signs will vary with the different forms of LGMD. In addition to proximal muscle weakness, there may or may not be:

- Distal muscle weakness.
- Muscle hypertrophy.
- Contractures.
- Involvement of the heart, respiratory muscles or tongue. (Facial weakness is not usual.)
- Variation in the clinical expression of the condition, with clinical differences between individuals in one family.
- Variable age of onset and rates of progression. Also, note that the muscle weakness does not necessarily progress at a linear rate.

Usually there is no intellectual impairment.

See the table below (in 'Appendix') for details of the individual LGMD types and their clinical features.

Assessment

LGMD is relatively rare: consider more likely diagnoses first. Reaching a diagnosis involves combining information from the clinical presentation and various investigations, mainly serum creatine kinase (CK), muscle biopsy and genetic testing.

History

- Ethnic and geographical origin - certain LGMDs have been found in specific regions or countries.
- Family history.
- Neonatal history.
- Childhood development and motor milestones.
- Sporting ability.

Examination

- Ability to rise from the floor.
- Is there a finding (or history) of Gower's sign? This is seen in patients with proximal muscle weakness of the lower limb: when rising to stand, they use the hands as support, such that the hands 'climb up the legs'. This sign is common in Duchenne muscular dystrophy.
Spinal rigidity or scoliosis.
Muscle weakness, hypertrophy or contractures (including calf and tongue hypertrophy).

Note:
- The mode of presentation and the pattern of muscle involvement.
- Whether there are any additional clinical features.

**Interpretation of clinical patterns**
The precise clinical pattern and course can help identify the specific LGMD cause. For example:

- Neonatal hypotonia occurs in LGMD 1B.
- Contractures are most common in LGMD 1B.
- LGMD 2A - there is relative preservation of hip abductors and striking involvement of the posterior thigh muscles seen on MRI.
- LGMD 2A and LGMD 2C-F - scapular winging is characteristic.
- LGMD 2B - often have normal sporting ability until there is abrupt onset of symptoms.
- LGMD 1C - may have rippling muscle disease, characterised by signs of increased muscle irritability, such as percussion-induced rapid contraction, percussion-induced muscle mounding and/or electrically silent muscle contractions (rippling muscle).[9]

**Specialist centres**
- In the UK, the Newcastle Muscle Centre is the national LGMD diagnostic and advisory service.
- The Dubowitz Neuromuscular Centre in London provides a diagnostic and advisory service for congenital muscular dystrophies and congenital myopathies.[11]

**Investigations**[2, 8]
Key investigations are:

- Serum CK:
  - This is often raised in LGMD, but can be normal in some types.
  - Exclude non-muscle conditions first.
  - The degree of CK elevation helps distinguish between different types.

- Muscle imaging with CT or MRI - can show patterns of muscle involvement.[12]

- Muscle biopsy:
  - This is most useful on muscle which is affected clinically but is not 'end-stage'.
  - Analysed by immunohistochemistry and immunoblotting in an expert laboratory.
  - All LGMDs show dystrophic features with variations in fibre size, greater numbers of central nuclei and endomysial fibrosis.
  - Muscle biopsy immuno-analysis can suggest the diagnosis in many of the genetically defined types of LGMD.

- DNA analysis:
  - This is the 'gold standard' test, but its feasibility varies for different types of LGMD.
  - It requires a specialist laboratory.
  - For the rarer types of LGMD, this may only be available on a research basis.

In addition:

- Myoglobinuria can occur in LGMD2I.[1] It has been reported in a patient with sarcoglycanopathy.[13]
- Cardiac and respiratory investigations are often appropriate, to monitor for complications (see 'Complications and their management', below).

It is possible to reach a precise diagnosis in around 75% of the LGMD patients.

**Prenatal diagnosis**
**Genetic counselling** should be offered. If the specific subtype of LGMD can be identified, prenatal diagnosis or carrier testing for other family members may be possible.

**Differential diagnosis**
- Other muscular dystrophies.[8]
- Congenital myopathies.
- Dermatomyositis or polymyositis.
- Endocrine or metabolic myopathies, including Cushing’s syndrome and thyrotoxicosis.
- Spinal muscular atrophy.

**Management**[2]
There is no specific therapy for LGMD.\textsuperscript{[14]}

**Nondrug treatment**
- Physiotherapy to prevent contractures, using passive stretching, exercise therapy, ± orthoses.\textsuperscript{[15]}
- Exercise - the role of exercise in LGMD is controversial, but guidelines for other types of muscular dystrophy suggest gentle exercise within limits of comfort, and avoidance of prolonged immobility.
- Occupational therapy and aids such as a wheelchair, with careful attention to seating so as to minimise the development of scoliosis.
- Genetic counselling.
- Advice on benefits.
- Support groups (eg, Muscular Dystrophy Campaign).
- Monitoring for complications (see ‘Complications and their Management’, below).

**Possible drug treatment**
- Corticosteroids have been used in some patients with LGMD 2C-F, giving improvement in some reported cases.\textsuperscript{[2, 16]}
- A study involving two patients with dysferlin-deficient muscular dystrophy reported an improvement in muscle strength after treatment with rituximab.\textsuperscript{[17]}

**Complications and their management\textsuperscript{[2, 8]}**

Complications vary, depending on the specific LGMD and on individual variations in the clinical picture. Cardiac and respiratory surveillance are particularly important in LGMD 1B, LGMD 2C-F and LGMD 2I. Where the type of LGMD carries a high risk of cardiac or respiratory involvement, management should involve cardiac and respiratory physicians. This also applies in cases where the precise diagnosis is unknown.
Respiratory muscle weakness
This is most common in LGMD 2I and the sarcoglycanopathies. It leads to hypoventilation, which is often worse at night. Symptoms include frequent chest infections, morning headaches and daytime sleepiness. Management involves:

- Monitoring of forced vital capacity (FVC) - sitting and supine - and overnight pulse oximetry, which is helpful.
- Influenza and pneumococcal vaccines; prompt treatment of infections.
- Nocturnal home ventilation if required.
- Other respiratory support if required. See separate Duchenne Muscular Dystrophy article.

Cardiac complications
Dilated cardiomyopathy and/or conduction defects can occur in some forms of LGMD; they are common in LGMD 1B. Monitoring of cardiac function (under a cardiologist) is advised for LGMD 1B, LGMD 2C-F and LGMD 2I; or for where the LGMD type is unknown. Management involves:

- ECG and echocardiography as initial investigations.
- Standard management of heart failure.
- Management of arrhythmias - eg, anticoagulation, pacemaker, implantable defibrillator.
- If there is severe cardiac impairment with good respiratory function, cardiac transplantation may be appropriate.

Anaesthesia\[18\]
- Rarely, a malignant hyperthermic reaction to general anaesthesia can occur.
- Caution is needed regarding possible cardiac complications.
- As in any muscle disease, succinylcholine administration could cause life-threatening hyperkalaemia and should be avoided.

Musculoskeletal complications
- Contractures (eg, of the Achilles tendon) may require surgical release.
- Scoliosis - occurs mainly after wheelchair dependence. Careful attention to seating is important.
- Chronic pain can occur, and pain management should be part of care.\[19\]

Prognosis
This depends on the type of LGMD and whether there is cardiac or respiratory involvement. In general, all types of LGMD progress with time. However, this is highly variable between the different LGMD types and also between individuals with the same specific type or within a family. Also, the rate of progression is not necessarily linear.\[2\]

Research
Possible future treatments include:

- Antisense-mediated exon skipping - this is a promising therapeutic approach for Duchenne muscular dystrophy. It may be applicable to conditions caused by mutations in the dysferlin gene - eg, LGMD 2B and Miyoshi myopathy.\[21\]
- Gene therapy is a potential form of treatment.\[22\]

Appendix - summary of limb-girdle muscular dystrophy types and their clinical features

<table>
<thead>
<tr>
<th>Type of LGMD (and the protein involved, if known)</th>
<th>Usual age of onset (approximate)</th>
<th>Notable clinical features (in addition to proximal muscle weakness)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGMD 1A (myotilin)</td>
<td>Adulthood</td>
<td>• So far, this is described only in two families.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• May have nasal speech.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• May have cardiac and respiratory involvement.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• There are no contractures or muscle hypertrophy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• May have normal CK.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• May have distal muscle weakness.</td>
</tr>
<tr>
<td>LGMD 1B (lamin A/C)</td>
<td>Childhood</td>
<td>• May have neonatal hypotonia.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• There is usually slow progression.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cardiac involvement, including arrhythmias, is common and may be the only manifestation of the condition; may require an implantable defibrillator.</td>
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<tr>
<td></td>
<td></td>
<td>• May have respiratory involvement.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• May have distal muscle weakness and contractures.</td>
</tr>
</tbody>
</table>
**LGMD 1C** (caveolin 3)
- **Childhood - adult**
  - Early scoliosis; myopathy of the calf muscles (see ‘Presentation’ section).
  - Usually slow progression.
  - May have muscle hypertrophy and distal muscle weakness.
  - Extraocular muscle involvement has been reported in one case.\(^{[23]}\)

**LGMD 1D-F**
- **Adulthood**
  - This is very rare.
  - Proximal weakness with cardiac conduction defects and, later, dilated cardiomyopathy.
  - May have normal CK.

**LGMD 2A** (calpain 3)
- **Childhood (8-15)**
  - There is mainly proximal muscle weakness.
  - There is slow progression.
  - Muscle atrophy is prominent (notable sparing of the hip abductors).
  - Contractures are common.
  - Usually there is no cardiopulmonary involvement.
  - One case is reported as presenting with foot drop - aged 41.\(^{[24]}\)

**LGMD 2B** (dystrophin) also known as Miyoshi myopathy
- **Late teens, early 20s**
  - May have distal myopathy (Miyoshi myopathy).
  - Markedly elevated CKs.
  - Usually there is no cardiopulmonary involvement.
  - May have calf muscle pain and swelling.

**LGMD 2C-F** (sarcoglycan proteins)
- **Childhood**
  - There is a variable rate of progression.
  - Contractures may develop.
  - Cardiac involvement and respiratory involvement are common.

**LGMD 2G** (telethonin)
- **Childhood**
  - This is rare outside Brazil.
  - There is distal leg weakness.
  - May have cardiac involvement; there is no respiratory involvement.
  - May have normal CK.

**LGMD 2H** (TRIM 32)
- **Young adult**
  - This is rare outside Canada.
  - May have mild facial weakness.
  - May have cardiac involvement; there is no respiratory involvement.
  - May have normal CK.

**LGMD type 2I (fukutin-related proteinopathy)**
- **Variable**
  - This is relatively common in northern Europe. There is variable rate of progression.
  - May develop myalgia, myoglobinuria, contractures, muscle hypertrophy.
  - May have cardiac and respiratory complications - in some cases, the cardiac muscle is more affected than the skeletal muscle.\(^{[26]}\)
  - Diaphragmatic involvement may cause respiratory insufficiency while still ambulant.

**LGMD 2J** (titin)
- **Childhood**
  - So far, this is only reported in Finland.
  - May have cardiac involvement and distal myopathy.
  - Heterozygotes have a distal myopathy.

**LGMD 2K** (protein O-mannosyltransferase 1 (POMT1))
- **Childhood**
  - Severe learning difficulties and microcephaly.
  - Calf muscle hypertrophy.
  - A few cases have been described in Turkish and English families.

**LGMD 2L** (fukutin)
- **Childhood**
  - There is deterioration of weakness with viral infections.
  - May have cardiac and respiratory involvement.

**LGMD 2M**
- **Age 10-50**
  - There is asymmetric wasting of leg muscle (quadriiceps femoris).

**LGMD 2N** (POMT2)
- **Childhood (?)**
  - This has been described recently.
Further reading & references


2. EFNS guidelines on diagnosis and management of limb girdle muscular dystrophies; European Federation of Neurological Societies (2007).
10. Dubowitz Neuromuscular Centre; Great Ormond Street Hospital for Children.

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