

Limb girdle muscular dystrophy (generic term)

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Abstract

LGMD constitutes a group of genetically determined, progressive disorders of muscles, in which the pelvic or shoulder girdle musculature is predominantly or primarily involved. It may be inherited in an autosomal recessive or dominant fashion. The different subtypes of LGMD can now be distinguished by means of protein- and genetic analysis. All other diseases presenting with limb girdle weakness, (i.e. limb girdle syndromes) must be excluded when establishing the diagnosis. The clinical picture of autosomal recessive LGMD closely resembles that of Duchenne/Becker type of muscular dystrophy (DMD/BMD). In recessive families, disease onset beyond the early twenties is rare, but later onset may occur in dominant cases. Progression of muscle weakness is inevitable ranging from rapid to very slow. A survey in Netherlands using strict diagnostic criteria has reported a prevalence of 8.1×10^{-6} for all LGMD cases and 5.7×10^{-6} for autosomal recessive and sporadic cases. It is currently feasible to identify several subtypes of LGMD2 (autosomal recessive forms) on the basis of gene mutations and/or deficiency of gene products. No specific treatment is known and many patients receive physical therapy to prevent worsening of contractures. In the majority of patients, progressive weakness leads to disability requiring additional aids and adjustments.

Keywords

Limb girdle muscular dystrophy, LGMD, muscle weakness

Name of disease and synonyms

Limb girdle muscular dystrophy, LGMD, limb girdle dystrophy

Name of excluded diseases

All other diseases presenting with limb girdle weakness, i.e. limb girdle syndromes.

Diagnostic criteria/ Definition

LGMD constitutes a group of genetically determined, progressive disorders of muscle, in which the pelvic or shoulder girdle musculature is predominantly or primarily involved. It may be inherited in an autosomal recessive or dominant fashion. Onset may be at any age. In recessive

families onset beyond the early twenties is rare, but in dominant cases later onset can be seen. Progression of muscle weakness is inevitable but ranges from rapid to very slow. Serum CK activity is always elevated in autosomal recessive cases, in some dominant families it may be normal. Investigations such as electromyography and muscle biopsy usually provide evidence of non-specific myopathic or dystrophic changes. All other causes of a limb girdle syndrome have to be excluded¹.

Different subtypes of LGMD can now be distinguished by means of protein- and genetic analysis (see tables 1 and 2).

Table 1: Limb girdle dystrophies: Autosomal dominant

Subtype	Gene-product	Gene-localisation	Characteristic feature
LGMD 1A	Myotilin	5q31	Dysarthria ^{2,3}
LGMD 1B	Lamin A/C	1q21	Cardiac abnormalities ^{4,5}
LGMD 1C	Caveolin-3	3p25	Childhood onset ⁶
LGMD 1D	—	7q ^{7,9}	—

Table 2: Limb girdle dystrophies: Autosomal recessive

Subtype	Gene-product	Gene-localization	Characteristic feature
LGMD 2A	Calpain-3	15q15	Scapular winging ^{10,11}
LGMD 2B	Dysferlin	2p12	little shoulder girdle involvement, calf involvement ^{12,13}
LGMD 2C	γ-Sarcoglycan	13q12	Scapular winging, calf hypertrophy ¹⁴
LGMD 2D	α-Sarcoglycan	17q21	Scapular winging, calf hypertrophy ¹⁵
LGMD 2E	β-Sarcoglycan	4q12	Scapular winging, calf hypertrophy ¹⁶
LGMD 2F	δ-Sarcoglycan	5q33	Scapular winging, calf hypertrophy ¹⁷
LGMD 2G	Telethonin	17q11-12	With a anterior distal weakness, rimmed vacuoles ^{18,19}
LGMD 2H	TRIM32	9q31-q33	Slowly progressive ²⁰
LGMD 2I	FKRP	19q13.3	Calf hypertrophy, dilated cardiomyopathy ²¹
LGMD 2J	Titin ²²	2q31	—

Differential diagnosis

[Duchenne and Becker dystrophy](#) and manifesting carriers of these X-linked

dystrophies usually present with a limb girdle syndrome. These disorders are identified by dystrophin analysis in the skeletal muscle and DNA-Xp21 screening, which gives an accurate diagnosis in 90% of the cases²³. The karyogram should always be checked in female persons in order to rule out Turner syndrome, structurally abnormal X-chromosomes or X-autosome translocations. In some families restricted fragment length polymorphism analysis with probes within the *dystrophin* gene may be useful.

[Facioscapulohumeral \(FSH\) dystrophy](#) is inherited as an autosomal dominant trait. Facial muscles, although characteristically involved early in the disease, can be normal. This observation, and the fact that some cases may show limb girdle weakness at onset rather than a FSH distribution of weakness, may give rise to diagnostic confusion. Most families are linked to chromosome 4q, in 95% of patients deletions can be found²⁴. As yet no gene has been identified.

Some of the congenital myopathies may seemingly become manifest only in childhood or adult life and therefore confusion with LGMD may arise. The distinction is made by a meticulous history (early onset and floppiness) and muscle biopsy, showing characteristic structural changes of the muscle fibers²⁵.

Congenital muscular dystrophies often show hypotonia or generalized muscle weakness with multiple joint contractures at birth or in the first year of life, and a non-progressive or slowly progressive course^{26,27}. In merosin negative congenital muscular dystrophy linked to chromosome 6, the children are never able to walk and MRI of the brain shows prominent white matter changes, whereas intelligence is normal. [Merosin deficient muscular dystrophy](#) rarely also presents as a late-onset limb girdle syndrome²⁸. Equally rare are limb girdle muscular dystrophy and Duchenne muscular dystrophy presenting at birth²⁹. Another form of congenital muscular dystrophy is caused by mutations in the [fukutin-related protein gene \(FKRP\)](#), whereas mutations in the same gene cause the more benign LGMD2I^{21,30}.

In [Bethlem myopathy](#), molecular genetics disclosed mutations in two genes encoding for collagen type VI on chromosomes 21q22.3 and linkage to chromosome 2q37^{31,32}. It is an slowly progressive autosomal dominantly inherited myopathy manifesting with skeletal muscle weakness and contractures. The clinical onset is variable: prenatal with decreased foetal movements, neonatal with hypotonia and/or contractures, more frequently in early childhood with proximal weakness of the legs, but also in

adulthood and as late as the 6th decade with predominant limb girdle weakness.

[Miyoshi type muscular dystrophy](#) characteristically presents with calf muscle weakness and highly elevated (>10x) serum CK activities. In the course of the disease weakness spreads to the thigh, pelvic girdle, biceps brachii, and deltoid muscles, respectively. In later stages distinction with LGMD might therefore be difficult. The disease has been linked to the LGMD2B locus on chromosome 2p. Now it is evident that both LGMD2B and Miyoshi myopathy are different phenotypes of the same genotype³³.

Scapuloperoneal syndromes may be either neurogenic or myogenic by nature and present with the distinctive clinical picture of proximal upper extremity weakness accompanied by involvement of the peroneal muscles. One family has been linked to chromosome 12³⁴.

Emery-Dreifuss muscular dystrophy (EDMD) can present as an [X-linked](#), [autosomal dominant](#), or [autosomal recessive](#) disorder. The disorder is characterized by early onset of elbow, Achilles tendons, and spine contractures, and presents with humero-peroneal weakness. Cardiac conduction abnormalities with dilated cardiomyopathy are characteristic features of this disease. LGMD1B is characterized by identical cardiac involvement in combination with limb girdle weakness, without early contractures. The diagnosis of X-linked EDMD can be confirmed immunocytochemically, or more reliably by identifying mutations in the *emerin* gene³⁵. Both autosomal dominant and recessive EDMD and LGMD1B are caused by mutations in the *lamin A/C* gene^{5,36}.

Metabolic myopathies, including glycogen storage diseases, disorders of lipid metabolism, and mitochondrial myopathies, often manifest with a limb girdle syndrome. These disorders should be differentiated readily from LGMD by assessment of enzyme activities in the appropriate tissue, McArdle ischaemic forearm test, and histological, enzyme-histochemical and biochemical investigation of a muscle biopsy specimen, and ultimately by mutation analysis.

Chronic autosomal recessive spinal muscular atrophy (types III and IV) is more difficult to distinguish from LGMD. The diagnosis is usually established by the histopathological examination of biopsied muscle and electromyography. The recent discovery of the *SMN* gene on chromosome 5 allows DNA analysis in 95% of the patients³⁷.

[Proximal myotonic myopathy \(PROMM\)](#), caused by an enlarged CCTG expansion in intron 1 of the *zinc finger protein* gene on chromosome 3, also presents with slowly progressive weakness

in a limb girdle distribution, with onset in the third or fourth decade. A detailed family history might reveal autosomal dominant inheritance, with cataract, cardiac death, and pacemaker implantation³⁸. Myotonia is clinically present in 55% of patients, with electromyographic examination it can be demonstrated in an additional 25% of patients³⁹.

Therapeutically very important disorders to differentiate are [polymyositis](#) and [dermatomyositis](#). The more rapid evolution of weakness, often reported myalgias and common involvement of pharyngeal muscles in both polymyositis and dermatomyositis and the characteristic rash in the latter are discriminating features. Excellent response to treatment with corticosteroids favours a diagnosis of poly- and dermatomyositis. Diagnostic confusion sometimes arises since LGMD may show extensive mononuclear cell infiltrates in muscle, and half of the polymyositis patients does not respond to therapy.

Other differential diagnostic possibilities include vitamin deficiency, carcinoma, sarcoidosis, weakness following rhabdomyolysis, neuromuscular transmission disorders, non idiopathic inflammatory myopathies, toxic and endocrine myopathies.

It remains very important to exclude all other possible causes of a limb girdle syndrome. In a detailed survey it became evident that 25% percent of patients had been misdiagnosed⁴⁰.

Incidence

In 1991, a world survey of population frequencies of inherited neuromuscular diseases was undertaken by Emery⁴³. The prevalence and incidence rates for mainly adult onset cases of limb girdle muscular dystrophy is estimated to 20-40 x 10⁻⁶. Autosomal recessive (Duchenne-like) muscular dystrophy of childhood appeared to be a rare disorder with a prevalence of less than 5 x 10⁻⁶. It is, however, commoner in certain Arabic communities in North Africa, in Switzerland, in certain inbred communities in North America originating from Switzerland, and in Brazil. It has been estimated that around 3-12% of isolated males diagnosed as having X-linked Duchenne muscular dystrophy may in fact have this clinically similar autosomal recessive disorder.

There were always some reservations in accepting these figures because until recently diagnostic criteria were too imprecise for a reliable epidemiological survey. As shown above, LGMD can be mimicked by a number of clinically similar neurogenic and myogenic conditions and therefore it has become clear that these data were artificially inflated. In the

Netherlands, using strict diagnostic criteria, a prevalence of 8.1×10^{-6} for all cases, and 5.7×10^{-6} for autosomal recessive and sporadic cases was calculated⁴⁰.

The frequency of sarcoglycanopathies among cases of autosomal recessive LGMD varies in the literature from 0-35%. The overall prevalence of primary sarcoglycanopathies in north east Italy, was estimated to be 5.6×10^{-6} . Investigations in Brazilian families suggest that 33% of the LGMD families are caused by mutations in the 15q gene, 33% in the 2p gene, 17% by mutations in the *adhalin* gene, and less than 10% can be ascribed to mutations at the 13q locus⁴². LGMD2I seems to account for a large proportion of patients who have previously been excluded from other LGMD disease loci²¹

Clinical description

Autosomal recessive LGMD

The clinical picture of autosomal recessive LGMD closely resembles that of Duchenne/Becker type of muscular dystrophy (DMD/BMD).

There is a variable age of onset although in most families the first symptoms occur in the first or second decade. Weakness of the limb-girdle muscles is first manifesting in the pelvic girdle, and is progressive. Involvement of the shoulder girdle muscles occurs about 2-10 years later. Some forms have a course similar to DMD, in which the ability to walk is lost around the age of 10 years. Other forms have a less rapid course, sometimes even without losing ambulence.

Calf enlargement is frequently seen, especially in sarcoglycanopathies. Facial involvement is unusual, although it may occur in late stages of the disease. Distal muscle involvement usually occurs in late stages, and is less prominent than proximal weakness, however in LGMD2G footdrop is a rather early observation, and in LGMD 2J wasting of the anterior tibial muscle.

The knee and biceps jerks often disappear first, whereas the ankle jerks are relatively spared. Achilles-tendon contractures are frequently observed but more extensive contractures are only encountered in severely disabled patients.

Intellectual functions are usually preserved. Pulmonary function decreases with deterioration of muscle strength autosomal recessive LGMD, sometimes leading to premature death.

Cardiac involvement occurs in about 20% in any type of sarcoglycanopathy (LGMD2C-F) LGMD2I due to mutations in the *FKRP* gene appears to have a frequent association with cardiomyopathy. There is no clear evidence for cardiac involvement in calpainopathy (LGMD2A) or dysferlinopathy (LGMD2B). LGMD2H (TRIM 32), LGMD2G (telethinopathy) and LGMD2J

(titin) have only rarely been described, and have as yet not been associated with cardiac abnormalities.

Autosomal dominant LGMD

There are several reports of families with evidence of autosomal dominant limb girdle dystrophy. Onset may range from childhood to the fourth decade. The course is usually relatively mild. Calf enlargement is sometimes seen. In an occasional family dysarthria and facial weakness were distinctive features of the disease. Distal involvement has been described in late stages of the disease, always less pronounced than proximal weakness. In a small proportion of the autosomal dominant families contractures of elbows, and plantar flexion of the ankles are conspicuous features early in the course of the disease. Pulmonary involvement seems to be related to the severity of the skeletal muscle weakness, and is therefore uncommon. Atrio-ventricular conduction disturbances necessitating pacemaker implantation are a key feature in LGMD1B. Because of the risk of sudden cardiac death despite pacemaker implantation, the necessity of intracardiac defibrillator implantation is now in analysis. LGMD1A (myotilin) and LGMD1C (caveolin) have not been associated with cardiac problems.

Management

No specific therapy is known. Patients should be counseled about the inheritance pattern and the course of this disorder. Many patients receive physical therapy to prevent worsening of contractures although its efficacy has not been evaluated. In the majority of patients, progressive weakness leads to disability necessitating additional aids and adjustments, like a cane, home alterations, and wheelchair. In this stage of the disease referral to a rehabilitation physician should be considered. If patients become wheelchair-bound, involvement of the respiratory muscles must be monitored. The recommendations for cardiac surveillance in this group depend very much on the type of LGMD.

Prenatal diagnosis might be possible in cases/families with a known genetic defect. Whether the severity of the disorder warrants an abortion is an individual decision.

Contact with patient support groups is useful for individual patients.

Diagnosis

A large number of disorders present with weakness in a limb girdle distribution. Currently it is feasible to identify several subtypes of LGMD2 on the basis of gene mutations and/or deficiency

of gene products. Since screening for mutations is time consuming and linkage analysis which would indicate the location of the affected gene, is only rarely informative because it requires large families, the importance of protein screening in the diagnostic process has to be stressed⁴³.

Genetic counseling

Limb girdle muscular dystrophy is inherited in either an autosomal recessive or dominant manner. In case of autosomal dominant inheritance each affected individual is at 50% risk of transmitting the mutation to each of his children, whatever their gender. In LGMD1B the manifestation of the disorder is variable within the same family.

In autosomal recessive forms each sib of an affected individual is at 25% risk of getting the disorder.

Prenatal diagnosis

Prenatal diagnosis might be possible in cases/families with a known genetic defect. Whether the severity of the disorder warrants an abortion is an individual decision.

Unsolved questions

There are still forms of limb girdle muscular dystrophy, in which all other possible causes of a limb girdle syndrome have been excluded, in which the causative gene is not yet known. In most other forms the exact mechanism that causes the disease is as yet unexplained, and genotype-phenotype correlations are not completely unravelled. Lots of work have to be done before a causative therapy can be given.

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