The Growing Family of Limb-Girdle Muscular Dystrophies: Old and Newly Identified Members

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Limb-girdle muscular dystrophies (LGMD) are an extremely heterogeneous and rapidly expanding group of diseases characterized by progressive weakness of pelvic, scapular and trunk muscles with sparing of facial and distal musculature in most of the subtypes, onset in childhood or in adults of both sexes, very variable clinical severity ranging from mild to severe phenotypes, some associated with cardio-pulmonary and extraskeletal impairment and high serum creatine-kinase (CK) levels. In the past years, huge advances have been recorded in the various identification methods and new distinct entities were discovered. However, it is not yet clear why some muscle groups are affected and others spared in a specific subtype of LGMD, why similar clinical pictures are associated with different genes and mutations, while the same gene or mutation may present with very various clinical phenotypes [1]. In this review we summarize the main aspects of positive and differential diagnosis in LGMD.

Key words: Limb-girdle muscular dystrophies, calpain 3, dysferlin, anoctamin 5, γ, α, β and δ sarcoglycans.

OVERVIEW

LGMD have been first defined in 1954 by Walton and Natrass, but early description of LGMD dates back to the late eighteenth century, with the first observations and description of patients made by Erb and Leyden-Mobius [2]. The LGMD are caused, in our actual knowledge, by autosomal recessive or dominant mutations in many different genes encoding for distinctive types of proteins, with completely different functions, located in all muscle cell compartments: sarcolemma, nuclear membrane, sarcomere, cytosol or the extracellular space. Nowadays, we have 30 distinct LGMD subtypes and other entities are new candidates, so every year an updated classification table is published online. More than 90% of the cases are autosomal recessive in aetiology and are known as **type 2 LGMD**, subsequently classified with letters, in an alphabetical order, in chronological accordance to the order of their discovery. Less than 10% are **type 1 LGMD** (autosomal dominant) and we recognize now eight different subtypes, LGMD 1A-H, of which many were found in only few families. Obviously, soon the letters of the alphabet are going to be insufficient for the expanding recessive group [3-5].

ACTUAL CHALLENGES IN LGMD

Worldwide, is estimated that around 30% of the patients with obvious clinical picture of LGMD do not have an identifiable proteomic cause for their illness, complete understanding of the patho-physiology is lacking and the precise function of each of the implicated proteins, as well as the protein interactions in the complexity of muscle function are mostly unknown, prompting future research. Complete immunophenotyping and genotype analysis are not available everywhere, making the achievement of a precise diagnosis difficult, especially in sporadic patients, thus they require a comprehensive multiprofessional clinical evaluation and a complex laboratory approach. A precise positive and differential diagnosis in LGMD is essential, not only for prognostic purposes and early management of respiratory and cardiac complications, but also for genetic counseling, in waiting for future specific genetic therapies. A key aspect is also the psychological impact of a clearly established diagnosis for the patient and his family [6].

EPIDEMIOLOGY

LGMD are the fourth most common genetic muscle condition (after dystrophinopathies, faciosca-

pulohumeral muscular dystrophy and myotonic dystrophy) with a minimum prevalence of approximately 1/20000 in some countries, while in England, Mexico and Turkey LGMD are considered the second most common muscular dystrophy after dystrophinopathies, with a disease prevalence of up to 1/14500 and a carrier frequency of up to 1/150 [1, 4, 7, 8, 9].

Even among the subtypes, there are great differences between various populations. For instance, LGMD 2A is the most common form in some European countries like Spain, Italy, Czech Republic, Romania (personal observation), while in others, such as England or Denmark, LGMD 2I is the most prevalent type of LGMD. In Turkey and North Africa, as well as in Brasil, sarcoglycanopathies (LGMD 2C-2F) have a high relative proportion [10, 11, 4, 6, 12]. Some types of LGMD have been identified only in very few populations, for example LGMD 2J, a new form of LGMD was described in Finland and LGMD 2H was observed only in Manitoba Hutterites until now [13-16].

The global prevalence of the different LGMD subtypes is still difficult to accurately establish due to the fact that while some countries published detailed population studies of patients with diverse genetic muscle diseases including LGMD, many others, including Romania, only had sporadic reports of cases and no cohort study. The major advances in immunohistochemistry, immunoblotting and especially in the field of molecular genetics with the new techniques of whole exome sequencing are soon going to improve the current situation and our knowledge.

CLINICAL ASPECTS IN LGMD

A thorough clinical examination is essential for directing futher investigation and all types of LGMD share the same predilection for proximal shoulder and pelvic girdle musculature, but involvement of distal muscles is also present in some cases. The onset age is very variable, even in patients with the same mutation, from neonatal to middle age (usually in late childhood or early adulthood) as well as the disease course. In most cases, the weakness starts in the pelvic girdle and spreads to the trunk and shoulder muscles. The autosomal dominant subtypes start later and have a slower progression, but there are exceptions. Weakness and atrophy involve certain muscle groups with sparing of others and produce characteristic appearances: scapular winging, anterior axillary fold or

dropped shoulders, excessive lombar lordosis and waddling gait [6]. The selective involvement of different muscles in different subtypes has not been understood yet.

Pseudohypertrophy of the calf musculature or other limb muscles may be present in some of the recessive subtypes, like LGMD 2C-F, 2I and may lead to a wrong diagnosis of dystrophinopathy. Muscle tendon reflexes, preserved in early stages, are later lost.

Cardiac involvement in the form of dilated or hypertrophic cardiomyopathy and dysrhythmias are present in LGMD 2C-F, 2I and 1B, subtypes that may also have respiratory muscle weakness with nocturnal hypoventilation.

Contractures are part of the early or late clinical picture in LGMD 1B and in a milder form in LGMD 2A. Rigidity of spine is frequent in LGMD 1B and sometimes can be seen in LGMD 2A, while scoliosis is most commonly encountered in sarcoglycanopathies.

Abnormalities of the central nervous system with mental retardation are rarely seen in LGMD 2I and 2K [4, 12].

AUTOSOMAL DOMINANT LGMD

LGMD 1A (5q) is caused by mutations in the gene for *myotilin*, a thin filament associated sarcomeric protein of the Z- band, that help stabilize and anchor thin filaments during sarcomere assembly. Several families were described around the world, suggesting a spectrum of phenotypic aspects, including proximal/distal weakness and dysarthria, tight Achilles tendons and cardiac involvement [17-19].

LGMD 1B (1q) is the result of mutations in LMNA gene, encoding for the *lamin A/C*, intermediate filaments of the nuclear lamina, in charge with the structural integrity of the inner nuclear membrane and nuclear pore complexes. Different mutations in the LMNA gene are associated with very diverse phenotypes. The early clinical features are mild proximal weakness starting in childhood and contractures, followed by cardiac abnormalities with arrhythmias, conduction disturbances and dilated cardiomyopathy leading to sudden death [20-22].

LGMD 1C (3p) is caused by mutation in CAV 3 gene, encoding for *caveolin 3*, a muscle-specific structural protein of the caveolae, invaginations of the plasma membrane essential in cellular trafficking and interacting with dysferlin. Mutations of CAV 3 gene are also associated with the rippling muscle disease, with a form of distal

myopathy and with idiopathic and familial isolated hyperCKemia. In LGMD 1C mild muscle weakness, cramping, and calf hypertrophy start in the first years of life [23-29].

LGMD 1D (6q), sometimes classified as 1E, is the result of defects in *DNAJB6* protein, a member of the heat shock protein 40/DNAJB family of molecular co-chaperone involved in protection from irreversible aggregation in protein synthesis and cellular stress. Onset is in middle adulthood with slowly progressive leg weakness with foot drop and no systemic features [3-5].

LGMD 1E (2q), in some classifications 1D, results from mutations in the *desmin* gene. Desmin is a vimentin-like major intermediate filament linking myofibrils to the sarcolemma, nucleus and mitochondria, involved also in mechanical and structural integrity and transmission of force. Desmin mutations lead to familial dilated cardiomyopathy with conduction defects and muscular dystrophy, with slowly progressive proximal weakness starting in the second decade or later, congestive heart failure, arrhythmia or sudden death. [4].

LGMD1F (7q), described in one large Spanish family, is due to mutation in TNPO3 gene coding for *transportin3*, a nuclear protein involved in protein transport into nucleus. Phenotypes of the family members were variable, with adult or juvenile onset of shoulder and pelvic weakness, but no cardiac involvement or contractures [30].

LGMD 1G (4p), described in a Brasilian family, results in dominant mutations in the gene for *heterogeneous nuclear ribonucleoprotein D-like protein (HRNPDL)* involved in RNA-processing events and linked with transportin 3. The disease has a homogeneous phenotype with variable onset age and proximal weakness, leg cramps and contractures with limited flexion of fingers and toes [31, 32].

LGMD 1H (3p) is a novel subtype of dominant LGMD with yet unknown protein product described in an Italian family with variable onset age and severity, slowly progressive proximal weakness and calf hypertrophy [33].

AUTOSOMAL RECESSIVE LGMD

LGMD 2A (15q) is a very frequent disease worldwide, first decribed by Fardeau *et al*. in the Reunion Island, caused by mutations in CAPN 3 gene, encoding for *calpain 3*, a non-lysosomal calcium-dependent cytosolic enzyme protein binding titin, involved in cytoskeletal remodeling and IkB α/NF-kB

pathway [34, 35]. Clinically, calpainopathy is characterized by early onset (between the ages 8-15, even later) of a symmetrical, selective atrophy of the proximal muscles with wasting of the musculature of the posterior compartment of the limbs, toe walking, scapular winging, early contractures of the elbows and calves and rarely calf hypertrophy. The intelligence is unaffected and heart dysfunctions are rare. LGMD 2A has a clinically wide variability both intra and interfamilial, with milder cases usually associated with missense mutations and more severe phenotypes with null mutations. CK level is high (still not as high as in dystrophinopathies, LGMD 2C-F or 2B), but reports of cases with normal serum CK suggest that a normal CK should not rule out a suspected LGMD 2A [10, 12].The life expectancy of the patients is close to normal. In the Romanian population, LGMD 2A is apparently the most frequent type of LGMD, with onset in childhood and middle adulthood, both in males and females. The patients (n = 11) were diagnosed based on clinical and pathological means using IHC and WB techniques, but further genetic tests are needed to confirm and evaluate the mutational spectrum of CAPN 3 gene in our country.

LGMD 2B (2p) is associated with defects in the DYSF gene, encoding for the sarcolemmal protein *dysferlin* involved in membrane fusion, myogenesis or vesicle trafficking events. Dysferlinopathies include Miyoshi myopathy, a distal muscle disease affecting the gastrocnemius and LGMD type 2B [36, 37]. The disease has been identified in many countries, including Romania. The symptoms start in the late teens with distal or proximal weakness, in some of the patients with predominant anterior compartment distal weakness and inability to walk on tiptoes. A subacute presentation may be seen in ¼ of the patients simulating an inflamematory myopathy, both clinically and morphologically. The clinical picture is generally milder than in other AR-LGMDs and progression is slow. Calf hypertrophy can rarely be present, as well as rigid or lax spine. Early loss of Achilles tendon reflexes is also a disease feature. Serum CK level is always very high. Cardiac and respiratory muscles are not affected and intelligence is normal.

LGMD 2C-F (13q, 17q, 4q, 5q) are caused by mutations in the genes for, respectively, *γ, α, β and δ sarcoglycans*, a complex of dystrophin-associated glycoproteins located in the sarcolemma, providing support against physical damage and signaling functions for the membrane. Sarcoglycanopathies are relatively severe diseases with

Duchenne-like clinical picture, early onset in childhood, high CK levels and frequent cardiac and respiratory complications. Milder cases are also seen, with a Becker-like phenotype [12, 38-40]. In Romania we identified three cases of γ sarco-glycanopathy using IHC and WB.

LGMD 2G (17 q) is the result of mutations in the gene for *telethonin*, a sarcomeric protein localized at the Z- band, interacting with titin, with roles in myofiber assembly. This rare subtype of AR-LGMD is associated with early onset (in teens) of marked proximal weakness, loss of ambulation at the end of the third decade and sometimes cardiac complications. CK levels are 3-30 fold increased [41].

LGMD 2H (9q) has the genetic defect in TRIM 32, tripartite-motif containing gene 32. The *TRIM 32* protein is a E3-ubiquitin ligase localized at the Z line, involved in labeling of proteins with ubiquitin for proteasome degradation. This form of LGMD, until now only found in Manitoba Hutterites in Canada, is a mild disease starting in the second or third decade of life with proximal slowly progressive weakness, without any cardiac involvement [42, 43].

LGMD 2I (19 q) is caused by mutations in the fukutin-related protein gene *FKRP* and is allelic with severe forms of congenital muscular dystrophy with muscle hypertrophy and normal CNS (MDC 1C). FKRP is ubiquitous, located in the Golgi apparatus and associated with dystro-glycan processing. In UK LGMD 2I is the most frequent type of LGMD, but still considered under-diagnosed. The spectrum of FKRP-related phenotypes is much more diverse than in other LGMD and the main differential diagnosis is dystrophinopathy, due to the similar pattern of predominantly proximal pelvifemoral weakness, calf hypertrophy, very high CK level and severe cardiac and respiratory complications. There are also asymptomatic patients until late adulthood [44-47].

LGMD 2J (2q) is due to rare homozygous mutations in the gene for *titin*, while heterozygous states lead to AD tibial dystrophy. Titin is a giant structural sarcomeric protein binding calpain and telethonin and playing an important mechanical, developmental and regulatory role. Clinically, the onset is in childhood with proximal weakness, anterior tibial wasting but no cardiac abnormalities [48].

LGMD 2K (9q) was described in Turkish families with mutations in POMT 1 gene and associates early mild proximal weakness, micro-cephaly, mental retardation and high CK level. *POMT1 (protein O-mannosyltransferase 1)* is an enzyme that catalyzes O-mannosylation of proteins [5, 49].

LGMD 2L (11p) is caused by mutations in ANO 5 encoding for *anoctamin-5*, a calcium-activated chloride channel with yet unknown function. In Central and Northern Europe, anoctaminopathy is apparently a frequent type of dystrophy with variable age of onset from 20-60 years, variable phenotype with asymmetric atrophy of quadriceps or in the form of nondysferlin Miyoshi myopathy, muscle pain, calf atrophy and inability to stand on toes. Asymptomatic patients with elevated CK were also described [50-62].

LGMD 2M (9q) is the result of mutations in the fukutin gene, the same involved in Fukuyama congenital muscular dystrophy, and have early age of onset, weakness of the leg, calf hypertrophy, high CK level, inflammatory changes on muscle biopsy and improvement with steroids [63, 64].

LGMD 2N (14 q) is the expression of mutations in the gene for *POMT 2 protein (*O- manno-syltransferase 2 protein), associated with endoplasmic reticulum. Mutations in POMT2 gene were also linked with a type of congenital muscular dystrophy with brain abnormalities. Other mutations are associated with a mild limb-girdle phenotype, elevated CK and absence of brain involvement. Defects in glycosylation of α dystroglycan cause several forms of LGMD [63, 65].

LGMD 2O (1p) due to *POMGnT1* (O-linked mannose β1 2-N-acetylglucosaminyltransferase) gene mutation, had been described in a patient with proximal weakness, hypertrophy of calves and quadriccaps, wasting of hamstrings, early loss of ambulation and high CK [66-68].

LGMD 2P (3p) is due to mutations in the gene for *dystrophin-associated glycoprotein 1 (DAG 1)*, starts in the first decade with slowly progressive weakness and mental retardation [66, 69, 70].

LGMD 2Q (8q), caused by mutations in *plectin*, a sarcolemmal protein interacting with dystrophin and β dystroglycan, lead to early stable generalized weakness, delayed walking, progressive course in teens, atrophy of muscles, very high CK level and loss of ambulation in adulthood [71].

LGMD 2R (2q), caused by recessive mutations in *desmin* have atrio-ventricular conduction blocks, proximal and facial weakness and respiratory involvement as main clinical features [72].

In LGMD 2S (4Q) mutations in *transport protein particle complex 1, subunit 11 (TRAPPC11)* cause a progressive proximal leg myopathy with early onset, scapular winging, fatigue, myalgia and involvement of the central nervous system [73, 74].

Several other newly described forms are waiting to be added to the list of recessive LGMD**: LGMD 2T**, caused by mutations in the *GMPPB* gene (GDP-mannose pyrophosphorylase B) associated with congenital muscular dystrophies due to hypoglycosylation of α-dystroglycan and also with a new type of LGMD, described so far only in three patients with mental retardation and dystrophic finding on the muscle biopsy [75].

Another newly identified type is **LGMD 2U**, related to some particular alleles of the isoprenoid synthase domain containing gene and causing a severe Duchenne-like phenotype [76].

MORPHOLOGICAL AND IMMUNOHISTOCHEMICAL ASPECTS IN LGMD

The morphological picture in LGMD can be appreciated on muscle cryosections using histological, histochemical and enzyme histochemical techniques showing a more or less pronounced dystrophic pattern with a different amount of variation in the fibre size, round or polygonal atrophic and hypertrophic fibres, necrosis with or without phagocytosis, regeneration, splitting of fibres, lobulated fibres and fibrosis. In advanced stages, the muscle is partially or completely replaced by fat and connective tissue. The muscle biopsy must be made from a moderately affected muscle, thus require a prior thorough clinical examination and is better performed after image studies, to choose a muscle that is most imformative.

By itself the picture, useful for differential diagnosis with other muscular diseases, cannot differentiate between the various subtypes of LGMD, so a panel of antibodies is necessary for immunohistochemical and/or immunoblot assessment of frozen muscle tissue.
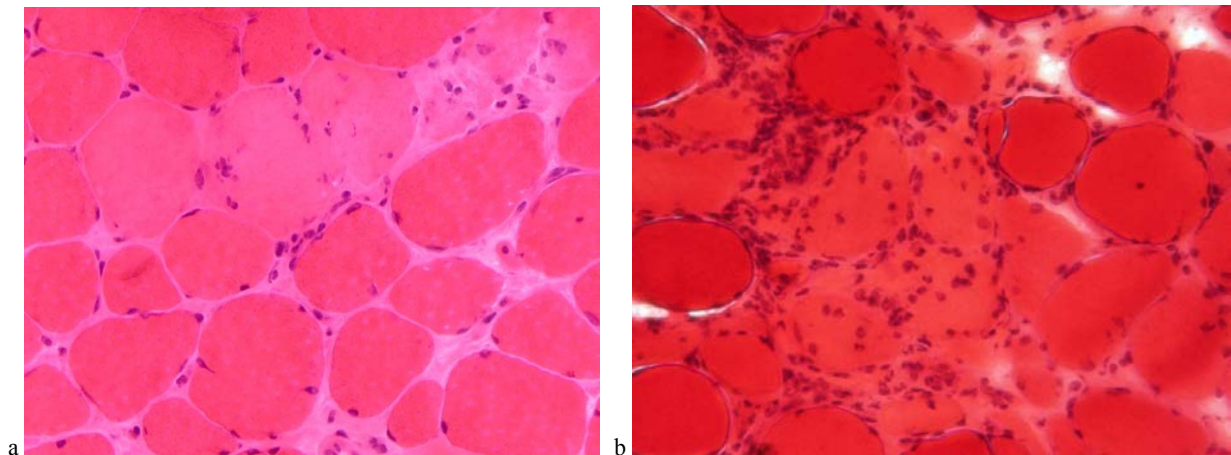

Figure 1. a Pale necrotic fibres in a case of LGMD 2A HE;
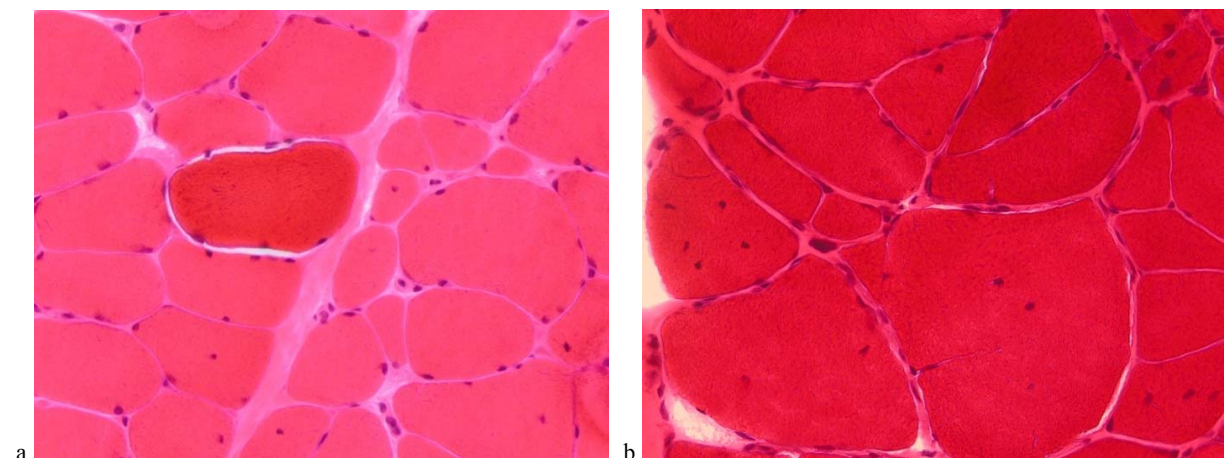b Necrosis with phagocytosis in a case of LGMD 2C. HE.

Figure 2. a. Variation in the fibre size and a hypercontracted fibre in LGMD 2A. HE;
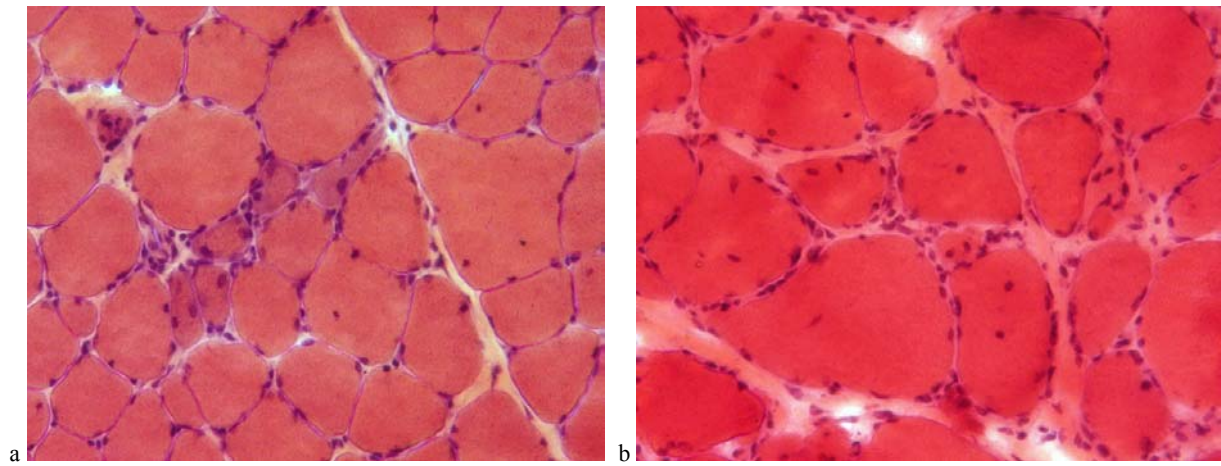b. Splitting of fibres in a case of LGMD 2A. HE.

Figure 3. a. A group of basophilic regenerated fibres. HE;
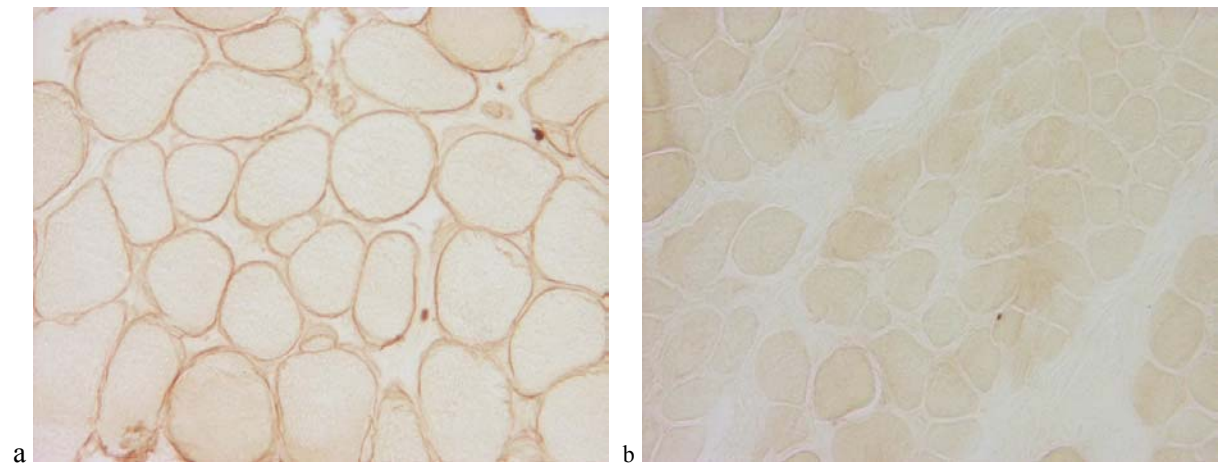b. Numerous internally located nuclei in LGMD 2C. HE.

Figure 4. a. Normal immunolabeling of γ SG in a case of LGMD 2A;
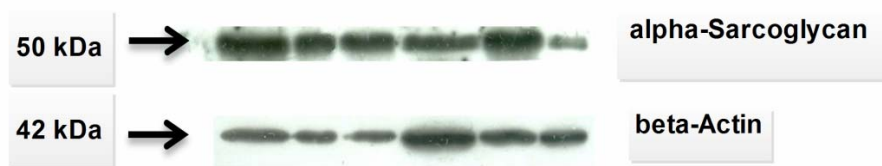b. Absence of γ SG on the sarcolemma in a case of LGMD 2C (γ SG, peroxidase).

Figure 5. WB: α Sarcoglycan (50 kDa) is present in all the muscular biopsies presented,
showing a slight reduction in the 6-th lane. β-Actin is shown at the 42 kDa molecular weight, as loading control.

Figure 6. WB: Calpain-3 (monoclonal mouse antibody) pattern in different muscular biopsies, showing a reduction
in lanes 1 and 2 for both Calpain-3 bands, at 94 and 60 kDa. On the same blot, β -Actin (polyclonal rabbit antibody)
is shown at the 42 kDa, as loading control.

Performance and interpretation of these tests require specialized and fully equipped laboratories, as not only primary, but also secondary reductions in protein expression can occur and may be difficult to interpret. This is particularly the case with the members of the dystrophin-associated glycoprotein complex. The protein analysis in close correlation with the clinical picture is a very important tool in directing further genetic tests and is considered a useful practice to analyze several proteins simultaneously [3, 77].

Table I
Morphological aspects in dominant L GMD

Type of LGMD	Protein	Characteristic pathological features	IHC /WB features
1A	Myotilin	D, Rimmed vacuoles with or without inclusions	IHC: Protein aggregates Secondary laminin- γ reduction
1B	Lamin A/C	Myopathic, Rimmed vacuoles, inclusions	Lamin A/C normal expression Secondary laminin- β1 reduction
1C	Caveolin 3	D, on EM loss of caveolae at the sarcolemma	IHC, WB: Absence/reduction of caveolin 3 Secondary reduction of dysferlin
1D	DNAJB6	D, Rimmed vacuoles, eosinophilic cytoplasmic body	-
1E	Desmin	Granulofilamentous inclusions – subsarcolemmal and perinuclear	-
1F	Transportin 3	D, Rimmed vacuoles	Increased desmin expression - some fibers
1G	HRNPDL	D, Rimmed vacuoles, denervation-like	Vacuoles stain with sarcoglycans and dystrophin
1H	?	D, mitochondrial abnormalities	

D- dystrophic

Table II
Morphological aspects in recessive LGMD

Type of LGMD	Protein	Characteristic pathological features	IHC /WB features
2A	Calpain 3	D, Lobulated/trabeculated fibres, eosinophils, neurogenic-like atrophy	WB only: reduction/absence of calpain 3, may be normal Secondary reduction of dysferlin in ½ of the cases
2B	Dysferlin	D, sometimes inflammatory infiltrates T-cells and macrophages	Complete absence or reduction of dysferlin Secondary reduction of calpain 3 and/or caveolin 3, aquaporin -4
2C	γ Sarcoglycan ,	D	Absence of γ SG, reduction of the other SG
2D	α Sarcoglycan	D	Absence of α SG, reduction of the other SG
2E	β Sarcoglycan	D	Absence of β SG, reduction of the other SG
2F	δ Sarcoglycan	D	Absence of δ SG, reduction of the other SG
2G	Telethonin	D, rimmed vacuoles, lobulated fibres	Absence of telethonin
2H	TRIM 32	mild D	
2I	FKRP	D, inflammatory infiltrates	Reduction of α dystroglycan, merosin
2J	Titin	Myopathic	WB: Reduction of calpain 3, C-terminal titin fragments
2K	POMT 1	Variation in the fiber size	-
2L	Anoctamin 5	D, inflammation, amyloid	Reduction of dystrophin, calpain 3 in some cases
2M	Fukutin	D, inflammation	Reduction of α dystroglycan, merosin
2N	POMT2	D	Reduction of α dystroglycan
2O	POMGnT1	D	α dystroglycan present, variable intensity
2P	DAG 1	D	Reduction of α dystroglycan
2Q	Plectin	D	Absence/reduction of sarcolemmal plectin labeling
2R	Desmin	Mallory body- like inclusions/subsarcolemmal deposits	Dystrophin and desmin accumulation
2S	TRAPPC11	Myopathic	D - dystrophic picture-

DIFFERENTIAL DIAGNOSIS IN LGMD

The differential diagnosis list in LGMD is both clinically and morphologically very broad and include more common and even potentially treatable diseases in internal medicine and rheumatology. Another important and challenging aspect is to differentiate between the numerous subtypes of LGMD, through clinical examinations, MRI imaging that can highlight preferential involvement of certain muscle groups with sparing of others depending on the type of dystrophy, morphological assessment of the biopsy, IHC and WB and genetic tests (Table III).

Table III
Differential diagnosis in LGMD

Disease	Specific aspects
Inflammatory myopathies (polymyositis, dermatomyositis, inclusion-body myositis-IBM)	More rapid evolution, more generalized weakness, spontaneous activity on EMG, inflammatory and other characteristic aspects on the muscle biopsy, serological tests, responsivity to immunosuppressive therapy
Dystrophinopathies (Duchenne, Becker, female manifesting carriers)	Pattern of inheritance Dystrophin gene mutations on DNA analysis Dystrophin expression abnormalities in muscle tissue using IHC and/or WB
Facioscapulohumeral dystrophy	Involvement of face, scapular, lower abdominal muscles, lumbar hyperlordosis, distal lower limb weakness Genetic tests available
Congenital myopathies (central core /multicore disease, nemaline rod myopathy, centronuclear, desmin myopathy, congenital fiber type disproportion)	Early onset usually Slowly progressive or relatively static weakness Characteristic histological and histochemical bioptical aspects and specific genetic tests
Glycogenosis and lipid myopathies	Histological, histochemical, enzyme histochemical features on muscle biopsy, α glucosidase enzyme activity
Mitochondrial myopathies	Multisystemic involvement, morphological and biochemical characteristics, specific molecular tests
Spinal muscular atrophies	More diffuse pattern of weakness, fasciculations, extremity tremor, neurogenic EMG and specific muscle biopsy aspects, normal CK, molecular tests
Endocrine and toxic myopathies	Clinical context, different age groups
Emery-Dreifuss muscular dystrophy	X-linked, early contractures, cardiac involvement, humeroperoneal weakness
Myotonic dystrophies (types 1 and 2)	Myotonia, facial and jaw weakness, ptosis in DM1 Distal weakness, myalgia, tremor, normal CK in DM2
Myasthenia gravis and congenital myasthenic syndromes	Fluctuating weakness and ptosis Neurophysiological tests, serum anti-acetylcholine and anti- Musk antibodies

CONCLUSIONS

Due to increasing complexity of diagnosis and management in LGMD, nowadays the main tasks are complete genotype-phenotype correlations in various populations, through concerted efforts involving many centres around the world and specialists in different fields which will lead to a better understanding of the molecular mechanisms underlying these disorders. It is assumed that these studies will be followed by the discovery and development of targeted therapies. An aspect of equal importance is also to increase awareness of physicians in different specialties on the existence and diversity of these diseases.

Distrofiile musculare forma centurilor reprezintă un grup de afecţiuni extrem de heterogen şi în rapidă expansiune, caracterizate prin deficit muscular pelvin, scapular şi la nivelul trunchiului, fără afectarea musculaturii faciale şi distale în majoritatea subtipurilor de boală, cu debut în copilărie sau în perioada adultă la ambele sexe şi cu severitate clinică extrem de variabilă de la fenotipuri uşoare la forme severe, unele asociate cu afectare cardio-pulmonară şi extrascheletală şi niveluri foarte crescute ale creatin-kinazei serice. În ultimii ani s-au înregistrat progrese uriaşe ale diferitelor metode de identificare şi au fost descoperite noi

entități distincte. Totuşi, încă nu este suficient de clar de ce există o afectare selectivă a unor grupe musculare cu lipsa de afectare a altora în diferitele subtipuri de boală şi de ce tablouri clinice similare se asociază cu gene şi mutaţii diferite, în timp ce aceleaşi gene şi chiar aceleaşi mutaţii se pot asocia cu fenotipuri foarte variate. În acest review sintetizăm principalele aspecte de diagnostic pozitiv şi diferenţial al distrofiilor musculare forma centurilor.

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