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Myofibrillar and distal myopathies

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ABSTRACT

Distal myopathies and myofibrillar myopathies are both rare subcategories of muscle diseases. Myofibrillar myopathies are genetically heterogeneous group of diseases characterized by distinctive histopathology of abnormal protein aggregations and myofibrillar disintegration. All genes causing myofibrillar myopathy encode proteins that either reside in or associate with the Z-disc. Distal myopathies are also genetically heterogeneous muscular dystrophies in which muscle weakness presents distally in the feet and/or hands. A subgroup of distal myopathies, desminopathy, distal myotilinopathy, ZASPopathy and alpha-B crystallin-mutated distal myopathy, belong to myofibrillar myopathies and show similar pathological changes in muscle biopsies. Common features of these diseases are dominant inheritance and adult-onset of symptoms starting in the feet and slowly progressing to encompass other muscle groups. Cardiomyopathy is not a common feature in distal MFM myopathies.

1. Introduction

Myofibrillar myopathies (MFM) are clinically and genetically heterogeneous group of progressive muscle diseases characterized by distinctive histopathology of abnormal protein aggregations and myofibrillar disintegration. Most of the diseases are autosomal dominant and adult-onset. In addition to the clinical presentation of distal weakness, muscle weakness can be proximal, proximo-distal or generalized, and can be accompanied by cardiomyopathy with or without respiratory insufficiency [1–3]. Causative mutations for MFM have been identified in seven genes: *DES*, *CRYAB*, *MYOT*, *FLNC*, *LDB3* (ZASP-protein), *BAG3*, and *PLEC* [4–10]. All of these genes encode proteins that either reside in or associate with the Z-disc, which is important in the maintenance of structural integrity of the sarcomere [11,12]. The known genes account for approximately half of identified MFM cases, indicating the underlying genetic cause has yet to be elucidated in many cases [13]. Features of myofibrillar pathology can also be observed in some other muscular dystrophies (Table 1).

Distal myopathy refers to muscle diseases in which muscle weakness presents distally and even in advanced state is more prominent in the feet and/or hands. There are over 20 genetically different entities identified, and still many distal myopathy families are without genetic characterization [14]. The inheritance pattern can be autosomal dominant or recessive. The age of onset is variable ranging from early

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Table 1 – Myofibrillar myopathies and myopathies that display myofibrillar features.

Condition	Gene/inheritance	Protein	Typical clinical phenotype	Distal presentation
Desminopathy	*DES*/AD (AR)	Desmin	Distal, proximal and scapuloperoneal forms	Yes
aB-crystallinopathy	*CRYAB*/AD	aB-crystallin	Proximo-distal muscle weakness	Not common
Myotilinopathy	*MYOT*/AD	Myotilin	Distal myotilinopathy	Yes
Filaminopathy	*FLNC*/AD	Filamin-C	Axial and proximo-distal muscle weakness	No
ZASPopathy (Markesbery-Griggs)	*LDB3*/AD	LIM domain-binding protein 3 (ZASP)	Distal myopathy	Yes
BAG3-related myopathy	*BAG3*/AD	BAG3	Proximal or proximo-distal muscle weakness	No
Plectinopathy	*PLEC*/AR	Plectin	EBS-MD, proximo-distal muscle weakness	No
MFM features				
HMERF titinopathy	*TTN*/AD (AR)	Titin	HMERF	Not common
LGMD1D	*DNAJB6*/AD	DNAJB6	LGMD1D	Not common

AD: autosomal dominant; AR: autosomal recessive; EBS-MD: epidermolysis bullosa simplex and muscular dystrophy; HMERF: hereditary myopathy with early respiratory failure; LGMD: limb-girdle muscular dystrophy; MFM: myofibrillar myopathy.

childhood to even late adulthood (Table 2). In distal myopathies, creatine kinase (CK) levels are normal or only mildly elevated with the exception of distal anoctaminopathy and Miyoshi myopahy in which the levels of CK are very high. Muscle imaging is useful in determining the distribution of affected muscles and the specific pattern can be diagnostic in some known entities [15]. Muscle pathology can vary, although rimmed vacuolar (RV) pathology is a common feature in many distal myopathies and more often without significant protein aggregation. In three of the MFMs, desminopathy, myotilinopathy and ZASPopathy, the presentation is frequently distal and hence pathological features in these distal myopathies are compatible with myofibrillar pathology [16–18]. MFM caused by mutations in CRYAB can rarely present as distal myopathy [19]. The diseases that are categorized into distal myopathies as well as MFMs are further discussed in more detail.

2. Myofibrillar myopathies with distinct histopathology

The MFM entity was described in the mid-1990s as a group of diseases sharing common morphologic features. They include myofibrillar disorganization beginning at the Z-discs, an abnormal accumulation of sarcoplasmic proteins, the presence of vacuoles and accumulated expression of multiple Z-disk proteins and dystrophin in the abnormal fiber regions. Staining with antibodies against desmin, aB-crystallin and myotilin are sensitive diagnostic tools to show pathological protein accumulations in MFM [20]. Rimmed and non-rimmed vacuoles are present in muscle fibers. At the ultrastructural level, there is disintegration of myofibrils that begins at the Z-disk [1,2,11,12]. Differences on electron microscopy might indicate certain subtypes of MFMs, although not always specific for the mutated protein [1,21]. For example, granulofilamentous material accumulating under the sarcolemma is considered a hallmark for desminopathy and aB-crystallin myopathy, and filamentous bundles in myotilinopathy and zaspopathy [21]. In addition, abnormal mitochondrial distribution has been observed in MFMs but not with a finding characteristic of conventional mitochondrial myopathies, i.e. multiple COX-negative or ragged red fibers. In MFMs, mitochondrial changes manifest as presence of rubbed-out fibers with lack of NADH, SDH or COX oxidative enzyme staining in larger cytoplasmic areas [12,22].

In addition to the above mentioned *MFM* genes, other disease entities can display pathological features similar to MFM and are sometimes included in the group of MFMs. Hereditary myopathy with early respiratory failure (HMERF) is caused by mutation in exon 343 (344 by new reference sequence) of A-band titin with the typical feature of respiratory failure in an ambulant patient [23–25]. Some findings in muscle biopsies of patients with HMERF overlap with MFM. However, the dark and hyaline changes in the cytoplasm on trichrome staining that are characteristics for MFM are not the main finding in HMERF. Instead, subsarcolemmal cytoplasmic bodies, frequently in a ''necklace'' distribution, that are abundant in HMERF are not a hallmark of MFM [24,25]. Mutations in *DNAJB6* gene cause limb-girdle muscular dystrophy 1D (LGMD1D) [26]. Muscle pathology in this disease shows some similarity to MFM, namely myofibrillar disintegration with small centrally located myofibrillar aggregates in the early stage of pathology These protein accumulations are present in scattered fibers and are smaller than in a typical MFM and rubbed-out fibers are not a common feature in LGMD1D. Instead, the pathology is dominated by the rimmed vacuoles in the later stages of the disease [27].

MFMs are associated with marked clinical variability. Muscle weakness in the lower limbs is the most frequent initial clinical symptom. The distribution of weakness varies and can be indicative for special subtype; predominant distal muscle involvement is typical for ZASPopathy, desminopathy and myotilinopathy, whereas proximal or mixed limbs weakness is typical for filaminopathy and aB-crystallinopathy [12]. The symptoms are slowly progressive and later generalized weakness including trunk and neck muscles is observed. The selectivity of muscle involvement on muscle imaging has been described in several subtypes of MFM [28,29]. CK levels are mildly to moderately elevated but normal levels do not overrule the possibility of MFM. Electromyogram (EMG) is typically myopathic with the possibility of spontaneous activity and myotonia [13]. Cardiomyopathy, usually dilated, and cardiac conduction defects are found particularly in