

Myofibrillar Myopathies

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Abstract

Myofibrillar myopathies (MFM) are a clinically and genetically heterogeneous group of neuromuscular disorders with a common morphological phenotype. MFM are morphologically characterized by myofibrillar structural changes comprising abnormal intracellular accumulations of the intermediate filament desmin and other proteins. The clinical manifestations are variable. The dominant clinical feature is usually a slowly progressive muscular weakness; in a subset of patients cardiomyopathy and peripheral neuropathy are present. Some patients have a rapidly progressive clinical course. A small proportion of MFM patients carry disease-associated mutations in the desmin, α B-crystallin, myotilin and ZASP genes. In most MFM patients, the molecular basis of the disease is unknown. There is no disease-specific therapy available.

Keywords

Myofibrillar myopathy, desmin, α B-crystallin, myotilin, cardiomyopathy.

Disease name

Myofibrillar myopathy, desminopathy, desmin related myopathy, desmin storage myopathy, protein surplus myopathies.

Definition

Myofibrillar myopathies (MFM) are a clinically and genetically heterogeneous group of sporadic and familial neuromuscular disorders with a common morphological phenotype. They are characterized by myofibrillar structural changes comprising abnormal intracellular accumulations of the intermediate filament desmin and other proteins. A small proportion of MFM patients carry disease-associated mutations in the desmin, α B-crystallin, myotilin and ZASP genes.

In most MFM patients, the molecular basis of the disease is unknown.

Epidemiology

Myofibrillar myopathies are very rare disorders; the exact frequency is unknown.

Clinical description

Clinical manifestations are variable. Onset of disease is in most patients in adulthood (50-60 years), but affected children have been described. Skeletal, cardiac and smooth muscle may be involved. Skeletal muscle symptoms comprise proximal and/or distal muscular weakness. Muscular atrophy may be present. Creatin-kinase (CK) is slightly increased in approximately 50% of the cases.

Electromyography shows electrical irritability (fibrillations, positive sharp waves, repetitive discharges). Myopathic and neurogenic motor unit potentials (MUPs) may be detectable. Cardiomyopathy is frequently associated, manifesting as arrhythmia, conduction defects or congestive heart failure. Cardiac symptoms may precede, follow or occur simultaneously to skeletal muscle symptoms. Involvement of respiratory muscles and peripheral neuropathy is seen in some patients (Selcen *et al.*, 2004; Selcen, 2004). In some patients a rapidly progressive severely disabling clinical course and death at young age has been reported (Dagvadorj *et al.*, 2004).

In a French family with a missense mutation in the α B-crystallin gene an earlier onset of disease, cataracts and involvement of respiratory muscles have been reported (Vicart *et al.*, 1998). Patients with myotilin mutations were reported to have a later onset of disease and an associated peripheral polyneuropathy (Selcen *et al.*, 2004). Despite these differences in genetic subsets, the clinical phenotype does not predict a specific genetic alteration in general.

Pathogenesis

Neither the etiology nor the pathogenesis of myofibrillar myopathies is yet completely elucidated.

Disintegration of the myofibrillar network beginning at the Z-disk is supposed to be the first step in the pathogenesis of MFM. In addition, abnormal accumulations of filamentous proteins e.g. desmin and α B-crystallin occur.

Desmin is the main intermediate filament protein in mature skeletal and heart muscle cells. In skeletal muscle it is located at the periphery of the Z-disk. It interconnects the entire contractile apparatus with the subsarcolemmal cytoskeleton, the nuclei, and other organelles. Mutant desmin has been shown to become assembly-incompetent and capable of disrupting the filamentous network (Dagvadorj *et al.*, 2004; Sjoberg *et al.*, 1999).

α B-crystallin is expressed in the lens, skeletal and cardiac muscle, lung, kidney and the nervous system (Bhat and Nagineni, 1989; Iwaki *et al.*, 1990) and serves as chaperone protein for desmin. Chaperone proteins bind unfolded and denatured proteins and thus avoid their unspecific aggregation. Mutated α B-crystallin has been shown to cause a similar form of myofibrillary myopathy as mutated desmin (Vicart *et al.*, 1998).

It is not yet clear to which extent myofibrillar disintegration and abnormal protein aggregations are caused by mutant proteins, abnormal protein phosphorylation, abnormal activation of degradative processes or by a

combination of these mechanisms (De Bleeker *et al.*, 1996; Nakano *et al.*, 1996; Selcen and Engel, 2003).

Molecular genetics

Mutations in the desmin, α B-crystallin, myotilin and ZASP (Z-band alternatively spliced PDZ motif-containing protein) gene have been described in patients with MFM. Additional candidate chromosomal loci without identified gene have been reported (for review see Selcen, 2004).

The desmin gene is located at chromosome 2q35. So far 21 different mutations have been identified (for review see Paulin *et al.*, 2004). In familial cases, autosomal dominant mode of inheritance has been described (Selcen *et al.*, 2004).

α B-crystallin is encoded by the *CRYAB* on chromosome 11q22.3. So far only 3 mutations have been described (Selcen and Engel, 2003; Vicart *et al.*, 1998).

Myotilin is encoded by *MYOT* and located at chromosome 5q31. So far 5 different mutations have been identified (Hauser *et al.*, 2002; Hauser *et al.*, 2000; Selcen and Engel, 2004).

The *ZASP* encoding gene is located at chromosome 10q22.3-10q23.2 (Faulkner *et al.*, 1999). In MFM patients so far 3 mutations have been described (Selcen and Engel, 2005).

Mutations are found only in a minority of patients with MFM, whereas in the majority no disease-specific mutations have been discovered yet.

Pathology

Muscle biopsies show myopathic changes comprising atrophic muscle fibres and fibre splitting. Endomysial inflammatory cells, necrotic or regenerating muscle fibres are infrequent.

The characteristic morphological feature is the presence of abnormal intracellular protein inclusions. The inclusions appear as single or multiple accumulations of amorphous material, small granules, spherical, lobulated or serpentine hyaline structures and/or cytoplasmic bodies (Goebel, 2002; Selcen, 2004). Some of the hyaline inclusions are congophilic.

Immunohistochemical analysis of the inclusions reveals beside desmin variable accumulations of other proteins such as α B-crystallin, myotilin, dystrophin, β -Amyloid precursor protein (β -APP), NCAM, filamentous actin, CDC2 kinase, plectin, prion protein, α 1-antichymotrypsin, gelsolin, ubiquitin, synemin, and nestin (De Bleeker *et al.*, 1996; Goebel *et al.*, 1994; Nakano *et al.*, 1997; Wanschitz *et al.*, 2002). Ultrastructural examination shows myofibrillar disintegration beginning at the Z-disk and dense bodies with granular and filamentous material (Fardeau *et al.*, 1978; Nakano *et al.*, 1996).

Morphologic features may overlap with those of other neuromuscular disorders, e.g. presence of rimmed vacuoles which are typically observed in inclusion body myopathy, and presence of ragged-red-fibres as in mitochondriopathies (Wanschitz *et al.*, 2002).

Diagnostic criteria

So far no clinical diagnostic criteria have been established. The diagnosis of MFM is based on the characteristic morphological features in the muscle biopsy.

Differential diagnosis

The principal clinical differential diagnoses are myotonic dystrophy and other muscular dystrophies, motor and sensory neuropathies and inclusion body myositis/myopathy (Selcen, 2004).

Diagnostic methods

Muscle biopsy.

Management including treatment

No specific therapy is available. Corticosteroids have not been shown to be of benefit. Physical therapy and other supporting devices are helpful in advanced cases (Selcen, 2004). Cardiac controls are recommended for detection of conduction defects and arrhythmias.

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