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, αB-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, αB-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, αB-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 αB-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 αB-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).
αB-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 denaturated proteins and thus avoid their unspecific aggregation. Mutated αB-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 Bleecker *et al.*, 1996; Nakano *et al.*, 1996; Selcen and Engel, 2003).

Molecular genetics

Mutations in the desmin, αB-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).
αB-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 αB-crystallin, myotilin, dystrophin, β-Amyloid precursor protein (β-APP), NCAM, filamentous actin, CDC2 kinase, plectin, prion protein, α1-antichymotrypsin, gelsolin, ubiquitin, synemin, and nestin (De Bleecker *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). Cardiologic controls are recommended for detection of conduction defects and arrhythmias.

References

Bhat SP, Nagineni CN. Alpha B subunit of lens-specific protein alpha-crystallin is present in other ocular and non-ocular tissues. Biochem Biophys Res Commun 1989; 158: 319-25.

Dagvadorj A, Olive M, Urtizberea JA, Halle M, Shatunov A, Bonnemann C, et al. A series of West European patients with severe cardiac and skeletal myopathy associated with a de novo R406W mutation in desmin. J Neurol 2004; 251: 143-9.

De Bleecker JL, Engel AG, Ertl BB. Myofibrillar myopathy with abnormal foci of desmin positivity. II. Immunocytochemical analysis reveals accumulation of multiple other proteins. J Neuropathol Exp Neurol 1996; 55: 563-77.

Fardeau M, Godet-Guillain J, Tome FM, Collin H, Gaudeau S, Boffety C, et al. [A new familial muscular disorder demonstrated by the intra-sarcoplasmic accumulation of a granulo-filamentous material which is dense on electron microscopy (author's transl)]. Rev Neurol (Paris) 1978; 134: 411-25.

Faulkner G, Pallavicini A, Formentin E, Comelli A, Ievolella C, Trevisan S, et al. ZASP: a new Z-band alternatively spliced PDZ-motif protein. J Cell Biol 1999; 146: 465-75.

Goebel HH, Voit T, Warlo I, Jacobs K, Johannsen U, Muller CR. Immunohistologic and electron microscopic abnormalities of desmin and dystrophin in familial cardiomyopathy and myopathy. Rev Neurol (Paris) 1994; 150: 452-9.

Goebel HH, Goldfarb L. Desmin-related myopathies. In Karpati G, editor, Structural and Molecular Basis of Skeletal Muscle Diseases, 1st edition. Basel; ISN Neuropath Press 2002: 70-73.

Hauser MA, Conde CB, Kowaljow V, Zeppa G, Taratuto AL, Torian UM, et al. Myotilin Mutation found in second pedigree with LGMD1A. Am J Hum Genet 2002; 71: 1428-32.

Hauser MA, Horrigan SK, Salmikangas P, Torian UM, Viles KD, Dancel R, et al. Myotilin is mutated in limb girdle muscular dystrophy 1A. Hum Mol Genet 2000; 9: 2141-7.

Iwaki T, Kume-Iwaki A, Goldman JE. Cellular distribution of alpha B-crystallin in non-lenticular tissues. J Histochem Cytochem 1990; 38: 31-9.

Nakano S, Engel AG, Akiguchi I, Kimura J. Myofibrillar myopathy. III. Abnormal expression of cyclin-dependent kinases and nuclear proteins. J Neuropathol Exp Neurol 1997; 56: 850-6.

Nakano S, Engel AG, Waclawik AJ, Emslie-Smith AM, Busis NA. Myofibrillar myopathy with abnormal foci of desmin positivity. I. Light and electron microscopy analysis of 10 cases. J Neuropathol Exp Neurol 1996; 55: 549-62.

Paulin D, Huet A, Khanamyrian L, Xue Z. Desminopathies in muscle disease. J Pathol 2004; 204: 418-27.

Selcen D, Engel AG. Myofibrillar myopathy caused by novel dominant negative alpha B-crystallin mutations. Ann Neurol 2003; 54: 804-10.

Selcen D, Engel AG. Mutations in myotilin cause myofibrillar myopathy. Neurology 2004; 62: 1363-71.

Selcen D, Engel AG. Mutations in ZASP define a novel form of muscular dystrophy in humans. Ann Neurol 2005; 57: 269-276.

Selcen D, Ohno K, Engel AG. Myofibrillar myopathy: clinical, morphological and genetic studies in 63 patients. Brain 2004; 127: 439-51.

Selcen D, Engel AG. Myofibrillar myopathies. In Engel AG, Franzini-ARmstrong C, editors, Myology. 3rd edn. New York; McGraw-Hill 2004: 1187-1202.

Sjoberg G, Saavedra-Matiz CA, Rosen DR, Wijsman EM, Borg K, Horowitz SH, et al. A missense mutation in the desmin rod domain is associated with autosomal dominant distal myopathy, and exerts a dominant negative effect on filament formation. Hum Mol Genet 1999; 8: 2191-8.

Vicart P, Caron A, Guicheney P, Li Z, Prevost MC, Faure A, et al. A missense mutation in the alphaB-crystallin chaperone gene causes a desmin-related myopathy. Nat Genet 1998; 20: 92-5.

Wanschitz J, Nakano S, Goudeau B, Strobel T, Rinner W, Wimmer G, et al. Myofibrillar (desmin-

related) myopathy: clinico-pathological spectrum in 3 cases and review of the literature. Clin Neuropathol 2002; 21: 220-31.