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.

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 denatured proteins and thus avoid their unspecific aggregation. Mutated αB-crystallin has been shown to cause a similar form of myofibrillar 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 mitochondrialopathies (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**

http://www.orpha.net/data/patho/GB/uk-MyofibrillarMyopathies.pdf