Case Report

Desmin-related myopathy: Report of a rare case

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The Protein Surplus Myopathies (PSM) are characterized by accumulation of protein aggregates, identifiable ultrastructurally, resulting due to mutations of the encoding genes. Desmin-related myopathies (DRM) are a form of PSM characterized by mutations of the desmin gene resulting in the formation of protein aggregates comprising mutant protein desmin and disturbance of the regular desmin intermediate network in the muscle fibers. We describe a rare case of DRM in a 23-year-old man who presented with complaints of difficulty in climbing stairs and running since the age of 5 years. EMG studies revealed a myopathic pattern. Muscle biopsy showed the features of muscular dystrophy with bluish rimmed vacuoles and sarcoplasmic inclusions, which were immunoreactive to desmin. Ultrastructural examination showed sarcoplasmic bodies and granulofilamentous inclusions. Although rare, the possibility of DRM/desminopathy should be considered in the presence of bluish rimmed vacuoles on light microscopy and characteristic ultrastructural inclusions. To the best of our knowledge this is the first case of DRM/desminopathy reported from India.

Key Words: Desminopathy, Desmin-related myopathy, Protein surplus myopathies, Congenital myopathies, Protein aggregating myopathies

Desmin-related myopathies (DRM) are a heterogeneous group of neuromuscular disorders characterized morphologically by abnormal focal accumulation of desmin within muscle fibers. These desmin aggregates can assume the forms of cytoplasmic body, granulofilamentous inclusions, and plaque-like deposits.[1]

The clinical presentation of DRM is heterogeneous. It commonly presents in adults and less frequently in children with weakness in the distal muscles but sometimes with proximal muscle weakness.[2] In addition, cardiac features and respiratory insufficiency may frequently be associated.

Case Report

A 23-year-old man presented with difficulty in running, climbing stairs and hopping since the age of 5 years. There was no history of similar illness in his family. Physical examination showed weakness of all groups of shoulder muscles and hip flexors and extensors. The creatine kinase enzyme level was 615 IU/L and electromyography showed myopathic pattern. Echocardiography and electrocardiography did not reveal any abnormality.

Muscle biopsy was done from the right vastus lateralis and conventionally divided into three portions for frozen, routine paraffin processing and electron microscopy.

Light microscopically, muscle biopsy showed significant variation of muscle fiber size, central location of nuclei, small atrophied fibers, endo- and peri-mysial fibrosis (Figures 1a and 1b). Some of the large and small fibers contained bluish-rimmed vacuoles with bluish tinged material (Figures 1c and 1d). In addition, occasional large muscle fibers also showed some densely eosinophilic stained material in the sarcoplasm (Figure 1e). Immunohistochemistry for desmin showed sarcoplasmic positivity in some of the muscle fibers (Figure 1f). Dystrophin (1,2,3), sarcoglycans (α, β, γ and δ), merosin, emerin and dysferlin were normally expressed, however there was non-specific staining with dystrophin in some of the muscle fibers.

Ultrastructural examination revealed two types of sarcoplasmic inclusions in the muscle fibers viz. sarcoplasmic or cytoplasmic body comprising electron dense core and radiating filamentous structures at the periphery with disruption of the inherent sarcomeres (Figures 2a and 2b). The other inclusions were granulofilamentous type consisting of a mixture of granular and filamentous material in the subsarcolemmal region (Figure 2c). The sections subjected for immunoelectronmicrocopy using desmin antibody revealed the deposition of gold particles in filamentous structures thereby confirming the desmin nature of these intermediate filaments (Figure 2d).

Discussion

Protein-Surplus Myopathies (PSM) are a group of familial or sporadic neuromuscular diseases characterized by abnormal non-lysosomal aggregation of proteins in a filamentous or non-filamentous fashion. These belong to the class of structural congenital myopathies. The current list of defined PSM

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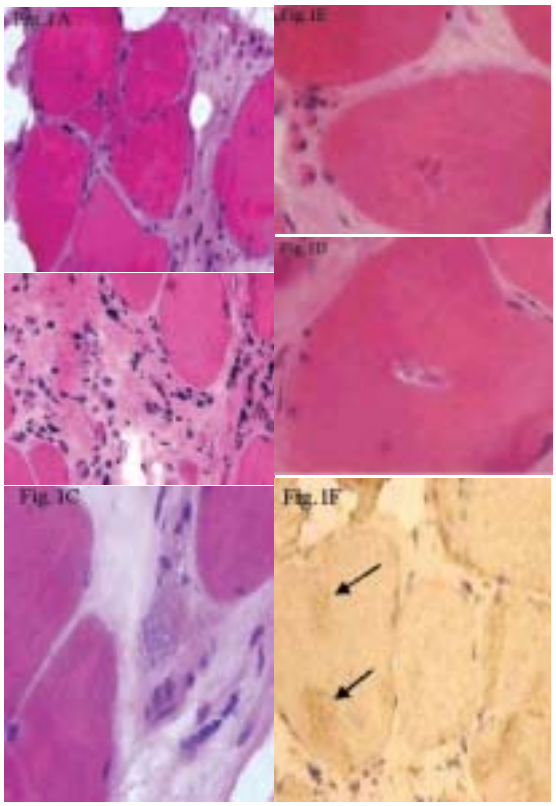
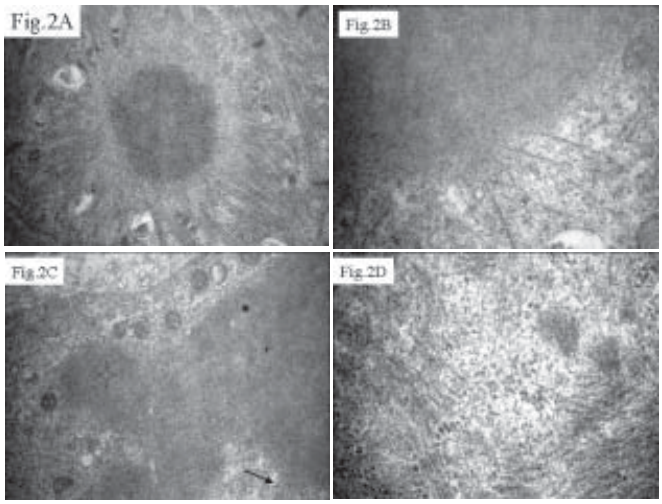


Figures 1a-1f: Photomicrographs showing variation in fiber size, center location of nuclei (a, H/E, x200) and numerous atrophied muscle fibers (b, H/E, x200). Some of the fibers contain bluish material (c, H/E, x200), rimmed vacuoles (d, H/E, x400) and cytoplasmic bodies (e, H/E, x400). Immunohistochemistry showing focal (arrow) sarcoplasmic desmin positivity (f, H/E, x200)

comprises DRM, actin myopathy, hereditary inclusion body myopathies and hyaline body myopathy. Hyaline body myopathy includes a small subset of myosin storage disorder due to mutations in MYH7.[3] However, some prefer to use the term 'myofibrillary myopathy' for DRM. In the true sense, myofibrillary myopathy is a generic term, which covers a wide spectrum of pathological changes, chiefly dissolution of myofibrils and subsequent accumulation of the products of myofibrillary degradation, which may assume different forms. On the contrary, DRM are a group of disorders, which are primarily characterized by accumulation of desmin and other substances with associated myofibrillary network disruption. Therefore, some authors regard DRM as a subtype of myofibrillary myopathy. The majority of myofibrillary myopathies are due to mutations in desmin and α-B-crystallin and in a small minority due to mutations in myotillin (though most of the mutations in myotillin are described in limb girdle muscular dystrophy (LGMD) Type Ia).[4]

Desmin, a 53-kDa protein belongs to Class III intermediate filaments, encoded by a gene located at Chromosome 2q35. It is subsarcolemmally located in the Z-band region and is linked to a protein called plectin. It is formed during myogenesis, partly overlapping with vimentin, which later disappears from the mature fibers. Desmin is now assumed to play a role in



Figures 2a-2d: Electron photomicrograph showing cytoplasmic body in the myofiber consisting of central electron dense core with peripheral radiating intermediate filaments (a, x8600; b, x13500) and granulofilamentous material in the subsarcolemmal region (c, x8600). Immunoelectron microscopy showing deposition of gold-labeled desmin particles in the radiating filaments (d, x13500)

maintaining the spatial relationship between the nucleus and the plasma membrane. Moreover, it has been presumed to participate in regulating myogenesis,[5] being more strongly expressed in immature rather than in normal mature myofibers.

To date, no human condition is known where desmin is absent but it is documented in knockout mice. Increase in desmin can be diffuse or focal. Diffuse increase of desmin is noted in immature muscle fibers, X-linked myotubular myopathy, neonatal myotonic dystrophy, and infantile spinal muscular atrophy.[6] Focal non-specific increase of desmin is seen in the periphery of lysosomal vacuoles in Type II glycogenosis[5] and in the perinuclear region in adult centronuclear myopathy.[6] Inclusion body-type accumulation of desmin is seen characteristically in DRM and non-specifically in some of the cases of Inclusion body myositis.

DRM are a group of PSM characterized by focal inclusion-body type accretion of desmin within the muscle fibers encountered both in childhood and adulthood. They can be sporadic or more commonly hereditary. Many patients also have cardiac involvement.[2] Earlier, based on the clinical presentation and mode of inheritance, three subgroups[1] of DRM have been described. However, with the recent identification of genetic defects in DRM, the distinction of different phenotypes based on genetic features is now preferred.[7]

It has been shown that desmin in DRM is hyperphosphorylated, but it has not yet been determined whether hyperphosphorylation[8] affects mutant or the wild-type desmin. It has been postulated that it is the mutant desmin, which forms the nidus for subsequent accumulation of normal desmin and other proteins. These proteins include dystrophin, β-amyloid, β-amyloid precursor protein, α-B crystallin, actin, α-actinin, nebulin, ubiquitin, gelsolin and α-

antichymotrypsin.

DRM may be subdivided into distinct molecular groups:

1. Mutations in the desmin gene: Missense mutations and deletions/insertions.[2] These are designated as desminopathies.
2. Mutations in the α-B crystallin gene.[9] Adult-onset myopathy, cardiomyopathy and cataract with granulofilamentous material rich in desmin and α-B crystallin also disrupting the intermediate filament network.
3. Other genetically defined DRM involving different gene loci including Chromosome 2q21, Chromosome 10q22.322, Chromosome 12[10] and chromosome 1p36 (Selenoprotein N gene locus).[11]

Genetic studies on this patient could not be done due to non-availability of these facilities in India. However, these are necessary for confirming the morphological findings and further characterization of the disease, since the clinical features of different sub-groups of DRM[2] are overlapping. Based on clinical, histomorphological, immunohistochemical, and ultrastructural features a diagnosis of DRM was preferred. Although rare, this possibility should be entertained in patients presenting with features of muscular dystrophy after the exclusion of minus proteinopathies.

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