Cardiovascular manifestations of myofibrillar myopathy

Miyofibriller miyopatinin klinik göstergeleri

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ABSTRACT

Myofibrillar myopathy (MFM) is a rare autosomal dominant disorder characterized by cardiac and skeletal myopathy. Either of these can dominate in the clinical picture. It is associated with cardiomyopathy, arrhythmia and/or atrioventricular (AV) conduction defects. Myofibrillar myopathy is often an overlooked disorder because of its variable clinical presentation. We highlight the various cardiovascular manifestations of MFM that have been reported in the literature and address the importance of considering this syndrome in young patients presenting with idiopathic cardiomyopathy and /or AV conduction defects. *(Anadolu Kardiyol Derg 2004; 4: 336-8)*

Key words: Myofibrils, desmin, cardiomyopathy

ÖZET

Miyofibriller miyopati (MFM) kardiyak ve iskelet miyopati ile karakterize olan nadir bir otozomal dominant hastalıktır. Klinik göstergeler arasında bu özelliklerden herhangi birisi egemen olabilir. Hastalık kardiyomiyopati, aritmi ve/veya atriyoventriküler (AV) ileti bozuklukları ile beraber görülebilir. Çeşitli klinik göstergeler nedeni ile MFM sık olarak gözden kaçırılabilen bir hastalıktır. Biz literatürde bildirilen MFM'nın kardiyovasküler göstergelerini ortaya koyduk ve idiyopatik kardiyomiyopati ve AV ileti bozuklukları ile başvuran genç hastalarda bu sendromun önemini vurguladık. *(Anadolu Kardiyol Derg 2004; 4: 336-8)*

Anahtar kelimeler: Miyofibril, desmin, kardiyomiyopati

There are few reported families with myofibrillar myopathy (MFM) worldwide (1-4). Clinically this disorder is characterized by cardiac and skeletal myopathy, either of these can dominate in the clinical picture. Histologically, it is characterized by non-hyaline lesions (foci of myofiber destruction) and hyaline lesions (myofibrillar residues) on light electron microscopy. However, because there is considerable clinical and pathological heterogeneity, the geno-phenotypical correlations are expected to be very difficult in MFM (5-6). Both neurological and histological evidences from skeletal muscle tissue in the presence of cardiomyopathy and/or atrioventricular (AV) conduction defects are usually sufficient to diagnose the disease even without endomyocardial biopsy (1). Myofibrillar myopathy and desmin related myopathy (DRM) are synonymously applied to a combination of familial myopathy and cardiomyopathy disorder (7). Application of immunohistochemical techniques has contributed to the term "desmin-related myopathies". Desmin is not the only protein that can be abnormally expressed with immuno-staining in patients with myopathy (8). However desmin is the main intermediate filament of skeletal and cardiac muscle fibers and certain smooth muscle cells; it plays an essential role in the maintenance of cyto-architecture by anchoring neighboring Z discs (9). Quantitative or qualitative abnormalities of Z-disk-associated proteins especially desmin causes abnormal mitochondrial behavior, disruption of muscle architecture, ends with fibre degeneration and fibrosis (10-12), excessive desmin (1,4), lacking of desmin (10-12), or mutation of desmin (13) and has been associated with different types of cardiomyopathy and variable degrees of myopathy. Mutation in desmin gene interferes with the normal assembly of desmin, it may be the cause of sporadic forms of MFM/DRM as 45% of patients do not report previous family history of the disease. Imunohistochemical evidence of desmin storage in either skeletal or cardiac muscles is available only in a minority of cases with this MFM/DRM. Three subgroups of MFM/DRM have been encountered and electromyography demonstrates myopathic features in each of the three types (11) as shown in Table 1. It preferentially affects distal skeletal muscles with variable degrees of severity, muscle group involvement and the age of presentation.

Cardiac features in MFM/DRM

Cardiac involvement is commonly present in the type I MFM. Different types of cardiomyopathies have been reported in association with DRM/MFM: 17 cases have been reported with restrictive cardiomyopathy (1,3,4,8,11,12,14-16) and three cases with hypertrophic cardiomyopathy (17-19). Arrhythmogenic right ventricular cardiomyopathy was found in one case

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(6). Selcen et al (20) described 63 sporadic cases with myofibrillar myopathy between 1977 and 2003, 16% of those cases had cardiomyopathies but they did not specify the types of cardiomyopathy. Furthermore, myofibrillar myopathies are clinically and genetically heterogeneous diseases, with common myopathological basis, which translate a process of myofibril degradation (20). Desmin cardiomyopathy is an unique variant of MFM/DRM (1), it has been applied specifically when certain criteria are fulfilled. It entails the presence of restrictive cardiomyopathy, disturbance of AV conduction and skeletal myopathy in the presence of granulofilamentous and desmin-immunoreactive material. In the state of Qatar we reported a Qatari family (21) with myofibrillar myopathy consisting of one brother and three sisters. The brother has restrictive cardiomyopathy and severe skeletal myopathy at the age of 16 years. One sister underwent heart transplantation for severe hypertrophic cardiomyopathy at the age of 15 years, the other sister had implantation of permanent pacemaker for complete heart block at the age of 21 years, and she has nearly normal echocardiographic findings. This is an unique family that presented with two different types of cardiomyopathy (restrictive and obstructive) in two young members of one family of the same generation. The progressive deterioration in clinical course is more commonly reported in affected males than females. Desmin inclusions have been recognized also in vascular smooth muscle (8) and smooth intestinal muscle (1), this underscores the systemic nature of this rare myopathy.

Arrhythmia and conduction system involvement in MFM/DRM

Atrioventricular block (AVB) of variable degrees has been recognized in eleven cases (1,3,8,19). The early manifestation of desmin accumulation may be atrioventricular conduction defects that were attributed to the depositions of desmin in the conduction system (18,21). Atrial fibrillation (AF) is the most frequent arrhythmia in MFM/DRM. Three out of six cases with arrhythmia had chronic AF in addition to history of recurrent ventricular tachycardia (2,8).

Coronary artery involvement

Cytoplasmic granulofilamentous inclusions within the smooth muscle of intramural coronary blood vessels have also been reported in patient with MFM/DRM (8).

Conclusion

Myofibrillar myopathy is a rare genetic disorder that should be considered in the differential diagnosis of idiopathic cardiomyopathy. Whether this condition is commonly overlooked or a rare condition is unknown and requires further epidemiological studies. High index of suspicion is needed for early diagnosis.

References

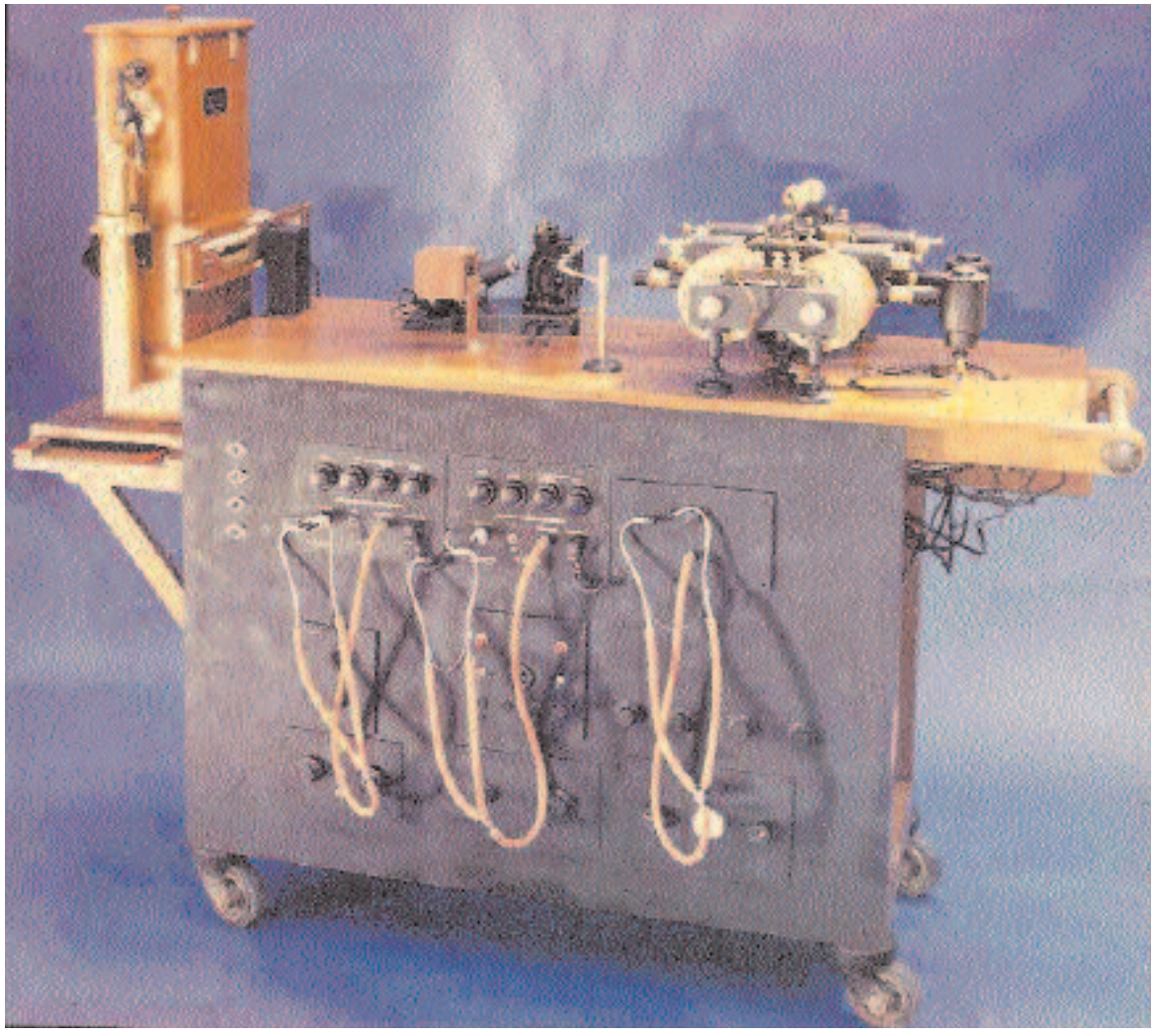
1. Arbustini E, Morbini P, Grasso E, et al. Restrictive cardiomyopathy, atrioventricular block and mild to subclinical myopathy in patients with desmin-immunoreactive material deposits. Jam Coll Cardiol 1998; 31: 645-53.
2. Vlay SC, Vlay LC, Coyle PK. Combined cardiomyopathy and skeletal myopathy: variant with atrial fibrillation and ventricular tachycardia. Pacing Clin Electrophysiol 2001; 24: 1389-97.
3. Porcu M, Muntoni F, Catani G, Mereu D. Familial cardiac and skeletal myopathy associated with desmin accumulation. Clin Cardiol 1994; 17:277-9.
4. Zachara E, Bertini E, Lioy E, Boldrini R, Prati PL,Bosman C. Restrictive cardiomyopathy due to desmin accumulation in a family with evidence of autosomal dominant inheritance. G Ital Cardiol 1997; 27: 436-42.
5. Olive-Plana M. Myofibrillar myopathies. Rev Neurol 2003; 37: 770-2.
6. Melberg A, Oldfors A, Blomstrom-Lundqvist C, et al. Autosomal dominant myofibrillar myopathy with arrhythmogenic right ventricular cardiomyopathy linked to chromosome 10q. Ann Neurol 1999; 46:684-92.
7. Ariza A, Coll J, Fernandez-Figueras MT, et al. Desmin myopathy: a multisystem disorder involving skeletal, cardiac, and smooth muscle. Hum Pathol 1995; 26:1032-7.
8. Abraham SC, DeNofrio D, Loh E, Minda JM, Pieta GG, Reynolds C. Desmin myopathy involving cardiac, skeletal and vascular smooth muscle: report of a case with immunoelectron microscopy. Hum Pathol 1998;29:876-82.
9. De Bleecker JL, Engel AG, Ertl BB. Myofibrillar myopathy with abnormal foci of desmin positivity II. immunocytochemical analysis. J Neuropathol Exp Neurol 1996; 55: 563-77.
10. Mavroidis M, Capetanaki Y. Extensive induction of important mediators of fibrosis and dystrophic calcification in desmin-deficient cardiomyopathy. Am J Pathol 2002; 160: 943-52.
11. Amato AA, Kagan CE, Jackson S, et al. The wide spectrum of myofibrillar myopathy suggests a multifactorial etiology and pathogenesis. Neurology 1998; 51:1646-55.

Table 1. Subtypes of DRM / MFM

Subgroup	Type I	Type II	Type III
Genetics	Autosomal dominant	Autosomal dominant	Autosomal recessive
Onset	Adulthood	Adolescence	Childhood
Desmin pattern	Granulofilaments	Cytoplasmic inclusions	Mallory body like inclusions
Distribution of deposits	Disseminated	Focal	Focal
Cardiac involvement	Constant	Occasional	Rare
Progression	Slow	Slow	Rapid
Skeletal myopathy	Distal muscle	Distal/proximal	Proximal/facial
Cause of death	Sudden cardiac death	Respiratory failure	Rapid death
Association	Smooth muscle disease	Dysphagia	Short course

DRM: desmin related myopathy, MFM: myofibrillar myopathy

12. Thornell LE, Carlsson L, Li Z, Mericskay M, Paulin D. Null mutation in the desmin gene gives rise to a cardiomyopathy. J Moll Cell Cardiol 1997; 29:2107-24.
13. Dalakas MC, Park KY, Semino-Mora C, Lee SL, Sivakumar K, Goldfrab LG. Desmin myopathy, A skeletal myopathy with cardiomyopathy caused by mutations in the desmin gene. N Engl J Med 2000; 342: 770-80.
14. Fidzianska A, Goebel HH, Osborn M, Lenard HG, Osse G, Langenbeck U. Mallory body-like inclusions in a hereditary congenital neuromuscular disease. Muscle Nerve1983; 6:195-200.
15. Bertini E, Bosman C, Ricci E. Neuromyopathy and restrictive cardiomyopathy with accumulation of intermediate filaments: a clinical, morphological and biochemical study. Acta Neuropathol 1991; 81:632-40.
16. Calderon A, Becker LE, Murphy EG. Subsarcolemmal vermiform deposits in skeletal muscle, associated with familial cardiomyopathy: report of two cases of a new entity. Pediatr Neurosci 1987; 13:108-12.
17. Sacrez A, Porte A, Batzenschlager A, et al. Myocardiopathie familiale. Etude de deux familles avec biopsies myocardique et musculaire. Arch Mal Coeur Vaiss 1979;72: 786-92.
18. Stoeckel ME, Osborn M, Porte A, Sacrez A, Batzenschlager A, Weber K. An unusual familial cardiomyopathy characterized by aberrant accumulations of desmin-type intermediate filaments. Virchows Arch Pathol Anat 1981; 393: 53-60.
19. Fardeau M, Godet-Guillain J, Tome FM et al. Une nouvelle affection musculaire familiale, definie par le accumulation intra-sarcoplasmique de un materiel granulofilamentaire dense en microscopie electronique. Rev Neurol 1978; 134: 411-25.
20. Selcen D, Ohno K, Engel G. Myofibrillar myopathy: clinical, morphological and genetic studies in 63 patients. Brain 2004; 127: 439-51.
21. El-Menyar A, Al Suwaidi J, Bener A. Clinical and histologic studies of a Qatari family with myofibrillar myopathy. Saudi Medical Journal 2004; 25: 447-50.



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