

Clinical and histologic studies of a Qatari family with myofibrillar myopathy

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ABSTRACT

The current study reports the first family with confirmed myofibrillar myopathy (MFM) in the Middle East and the third family worldwide. This study highlights the importance of considering MFM in young patients presenting with idiopathic cardiomyopathy, arrhythmia or atrioventricular block in the Gulf states. This is the first report that presented 2 different types of cardiomyopathy and 2 different indications of permanent pacemaker placement in the same generation of a family with MFM. This report studies a Qatari family consisting of one brother and 3 sisters. The brother had restrictive cardiomyopathy 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 permanent pacemaker for complete heart block at the age of 21 years. This report is focused mainly on the clinical presentation and investigations carried out for the brother including echocardiogram, cardiac catheterization, cardiac and skeletal muscle biopsy, and electromyography and electrophysiology studies. The study findings support the diagnosis of MFM.

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The Qatari population, similar to other Gulf countries, has family structures that are different from most of the world population. For example, there is of high rate of consanguinity in Gulf Countries. Therefore, the studied subjects were an ideal population for studying familial cardiomyopathies. Myofibrillar myopathy (MFM) is a rare autosomal dominant disorder characterized by cardiac and skeletal myopathy. Either of them can dominate the clinical picture. It preferentially affects distal skeletal muscles with variable degrees of severity, muscle group involvement and the age of presentation. It is associated with cardiomyopathy, arrhythmia or atrioventricular (AV) conduction defects. Myofibrillar myopathy is often an overlooked disorder as of its variable clinical presentation. It is also called desmin-related myopathy (DRM), when immunostaining of muscle

tissues is positive for excessive desmin deposition. Both neurologic and histologic evidences from skeletal muscle tissue in the presence of cardiomyopathy or AV conduction defects are usually sufficient to diagnose the disease even without endomyocardial biopsy.¹ In this study, we described a family with MFM.

Case Report. A 22-year-old Qatari male patient was admitted to the hospital with progressive shortness of breath, weakness and generalized anasarca over one year. The patient was doing well up to 6 years prior to the current presentation in 1996 when he was diagnosed with a tachy-brady syndrome requiring permanent pacemaker placement. One year later, he sustained a cardiac arrest secondary to several episodes of ventricular

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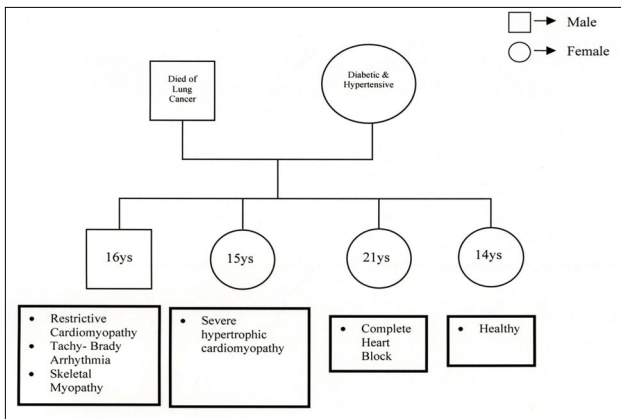


Figure 1 - The family tree demonstrates clinical presentation of the family in young ages. The boy has restrictive cardiomyopathy, arrhythmias and muscle disorders. The first sister has severe form of hypertrophic cardiomyopathy; the 2nd sister has complete heart block while the 3rd sister has no clinical disorders.

tachycardia, with severe hypokalemia (potassium level of 1.6mmol/L). From that time he became physically disabled and left his school. In April 2001, he was admitted with a new onset atrial flutter, which became a subsequently chronic event.

This patient has a striking family history (**Figure 1**). Of his 3 sisters, one underwent heart transplantation in 1989 for severe obstructive hypertrophic cardiomyopathy at the age of 15 years, based on echocardiographic and macroscopic examinations. Another sister had permanent pacemaker for complete heart block at the age of 21; both had no evidence of skeletal myopathy. The third sister is not known to have any chronic illness. His father died of lung cancer, his mother is diabetic and hypertensive. There was consanguinity of second degree between his parents.

A bedridden and cachectic male patient is alert and conscious with average intelligence. Cardiovascular examination revealed heart rate of 75beat/min, blood pressure 90/70mm Hg, mildly elevated jugular venous pressure and bilateral basal dullness. On auscultation, S1, S2, and systolic murmur on the lower left sternal border increases with inspiration. Abdominal examination showed mild ascites and hepatomegaly. He has mild facial muscle weakness, mild tongue base weakness and delayed swallowing. Upper and lower limbs examination showed massive lower limbs edema up to the sacrum. He has muscles weakness with distal muscle wasting while limbs sensation was intact. He has urinary incontinence. Laboratory investigations revealed evidence of chronic anemia, mild hypocalcemia and hypokalemia with no evidence of malabsorption. Serum creatinine kinase was normal.

Echocardiogram study. His most recent echocardiogram revealed a picture suggestive of

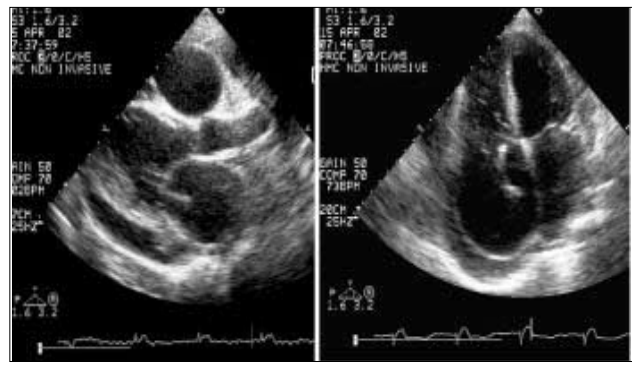


Figure 2 - The echocardiographic examination of the boy shows parasternal long axis and apical 4-chamber views. Both atria are enlarged, normal ventricular wall thickness and pericardial effusion.

restrictive cardiomyopathy (**Figure 2**) in addition to impaired systolic function of both ventricles and pericardial effusion.

Coronary angiogram and left and right catheterization with right ventricular biopsy studies. It revealed normal coronaries, normal left ventricle and elevated right ventricular end-diastolic pressure, with normal pulmonary artery systolic pressure. Pericardiocentesis with pericardial and myocardial biopsies were not diagnostic.

Respiratory study. Computerized tomography of the chest revealed compressive atelectasis secondary to pleural effusion, and pulmonary function test revealed restrictive pattern with evidence of diaphragmatic muscle weakness.

Histopathology and neurologic studies of the skeletal muscles. Electromyography revealed absent or low amplitude motor responses in the right upper and lower limbs, the right sural sensory response was absent; needle examination showed fibrillation potentials and mixture of motor unit potentials with mainly short duration, polyphasic motor unit potentials with rapid recruitment in all muscles but significantly worse distally. Those electro physiologic findings supported the diagnosis of chronic myopathy. The presence of fibrillation potentials suggested ongoing myonecrosis, fiber splitting or vacuolar inclusions. Biopsy of the left vastus lateralis indicated myofibrous degeneration; however, desmin stain was negative.

Discussion. The current study reported the first family with confirmed MFM in the Middle East and one of the few affected families worldwide.¹⁻⁴ This study highlighted the importance of considering MFM in young patients presenting with

idiopathic cardiomyopathy or AV block. This is the first report that presented 2 different types of cardiomyopathy (restrictive and obstructive) and 2 different indications of permanent pacemaker placement in 3 young members of one family of the same generation. As there is considerable clinical and pathological heterogeneity, the geno-phenotypical correlations are expected to be very difficult in MF⁵ and this may explain the findings in this family. The age of presentation in the current family is younger than those previously reported.^{1,6-9} The progressive deterioration in clinical course is more commonly reported in affected males than females, as was the case in our patients. Furthermore, our patient has unexplained significant pericardial effusion, and bipolar affective disorder that were not previously reported in such disorder. Myofibrillar myopathy and DRM are synonymously applied to a combination of familial myopathy and cardiomyopathy disorder.⁶ Application of immunohistochemical techniques has contributed to the term DRM; cardiac and skeletal myopathy may be associated with abnormal aggregation of desmin, lacking of desmin or even abnormal isoform of desmin.¹ Mutation in desmin gene interferes with the normal assembly of desmin and may be the cause of sporadic forms of MF⁵ and DRM as 45% of patients do not report previous family history of the disease.¹⁰ It may also explain the clinical heterogeneity in our current family. Desmin inclusions have been recognized also in vascular smooth muscle⁹ and smooth intestinal muscle;¹ this underscores the systemic nature of this rare myopathy. Three subgroups of MF⁵ and DRM have been encountered, electromyography demonstrates myopathic features in each of the 3 types, extremity muscle weakness markedly affecting distal limbs but facial and pharyngeal muscles can also be affected, and severe respiratory muscle weakness may also complicate MF⁵,^{11,12} our patient has weakness in the pharyngeal and diaphragmatic muscles beside distal muscle affection with recurrent chest infection secondary to repeated aspiration. Immunohistochemical evidence of desmin storage in either skeletal or cardiac muscles is available only in a minority of cases with this MF⁵ and DRM.^{1,13-14} Negative desmin stain as was the case in our patient does not interfere with the diagnosis of MF⁵. A limited number of cases were reported without the immunohistochemistry test but with unequivocal granulofilamentous deposits.¹⁵⁻¹⁷ Cardiac involvement is commonly present in type-I as was the case in our current study and the majority of reports.^{1,3} Different types of cardiomyopathy have been reported in DRM and MF⁵ as well as arrhythmia and AV conduction defects.^{1,9,14-18}

In conclusion, MF⁵ 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 epidemiologic studies. High index of suspicion is needed for early diagnosis, and subsequently permanent pacemaker or heart transplantation might be considered.

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