Case Series

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Cardiac Involvement in an Interesting Family of Myofibrillar Myopathy

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Abstract

Background: Myofibrillar myopathy primarily affects skeletal muscles; in some cases the heart muscle is also affected. The signs and symptoms of MFM vary among affected individuals, typically dependent on the exact genetic cause of the disease. Most people with this disease begin to develop muscle weakness (myopathy) in mid adulthood. However features of this disease can appear anytime between infancy and late adulthood. We here present a family of patients with history of muscle weakness and cardiac involvement.

Keywords: Myofibrillar myopathy, Muscle weakness, Cardiomyopathy, Desmin.

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Introduction

Myofibrillar myopathy (MFM) encompasses a genetically and clinically heterogeneous group of inherited or sporadic skeletal muscle disorders characterized pathologically by the presence of myofibrillar dissolution associated with accumulation of myofibrillar degradation products.

The term myofibrillar myopathy was proposed in 1996 as a non-committal term for a pathological pattern of myofibrillar dissolution associated with accumulation of myofibrillar degradation products and ectopic expression of multiple proteins that include desmin, αB- crystalline, dystrophin and congophilic amyloid material. Subsequent studies revealed dominant mutations in desmin and αBC in some MFM patients.

In the skeletal and cardiac muscles, normal desmin encircles the Z bands that hold together the actin filaments and help transmit tension along the myofibrils, protecting their structural integrity during repeated muscle contractures over time.

Defects in the function of desmin, as well as in the other desmin-associated filaments, may therefore cause fragility of the myofibrils and impair contraction causing Cardiomyopathy and Skeletal Myopathy.

The light microscopic features of myofibrillar myopathy were described in the 1970's and 1980s under such names as 'myopathy with inclusion bodies', atypical myopathy with myofibrillar aggregates', autosomal dominant cardiomyopathy with inclusions', cardioskeletal myopathy with intrasarcoplasmic dense granulofilamentous material', familial cardiomyopathy with subsarcolemmaldermiform deposits

Cardiomyopathy is present in 17% and is the leading cause of death among these patients.

Clinically it is characterized by slowly progressive weakness that can involve both proximal and distal muscles.

Distal muscle weakness is present in about 80% of individuals and is more pronounced than proximal weakness in about 25%, however only proximal muscle weakness is seen in 15-20% patients.

Myofibrillar myopathy is diagnosed by elevated creatinine kinase levels, ENMG, Nerve conduction study. However muscle biopsy is the ultimate which can clinche diagnosis

No specific treatment available for MFM. Management includes symptomatic and treatment of complications.

Case series study

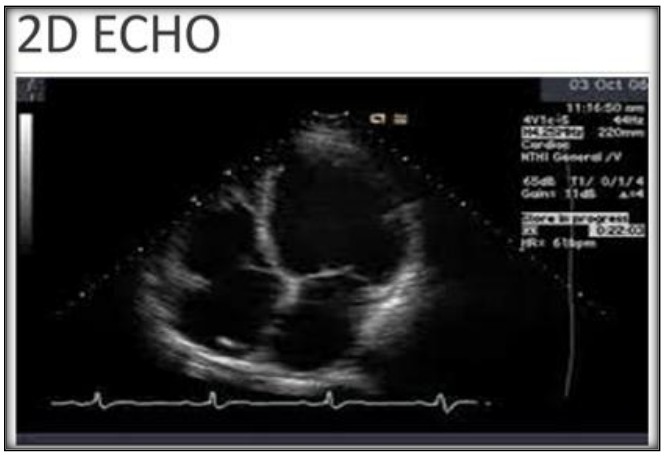
Case 1

42 year old male presented to us in 2012 with complaints of progressive difficulty in standing and walking, frequent falls and difficulty in getting up from squatting position. No Cranial Nerve/Visual difficulties. The above symptoms were of 2 years duration. In the year 2005, Patient had 2 episodes of Loss of Consciousness (? Syncope) and was evaluated. On further examination and evaluation, he was diagnosed to have a symptomatic third degree heart block. Following which he underwent a PPI (Permanent Pacemaker Implantation) at SJICS, Bangalore.

On examination- Alert, Fully conscious patient, Oriented to time and place. Hemodynamically Stable. No Cataract /

Fundus normal. Palatal Movements normal. No facial / jaw weakness. Bilateral Temporalis wasting present. Bilateral Sternocleidomastoid / Deltoid / Suprascapularis wasted. Small muscles of hand were normal. Upper limb power: Neck flexor 3/5, shoulder and elbow 4/5, Wrist 4/5. Lower limb power: Grade 4/5 at the hip and knee, ankle dorsifelxion & plantar felxion grade 2/5

Investigations- Routine Investigations were normal. Creatine Kinase – 1412 (elevated). Thyroid Functions were normal. EMG study of Right upper & lower extremeties suggest myonecrotic, myopathic process with significant myotonic discharges, findings consistent with myopathy. NCS - Mild reduction in



bilateral common peroneal nerve amplitude. In a few months, Patient developed persistent cough, dyspnoea with orthopnea. ECG revealed conduction abnormalities (tri fascicular block) with AF. 2D ECHO revealed Dilated Cardiomyopathy with severe LV dysfunction of 15-20%. (Figure 1)

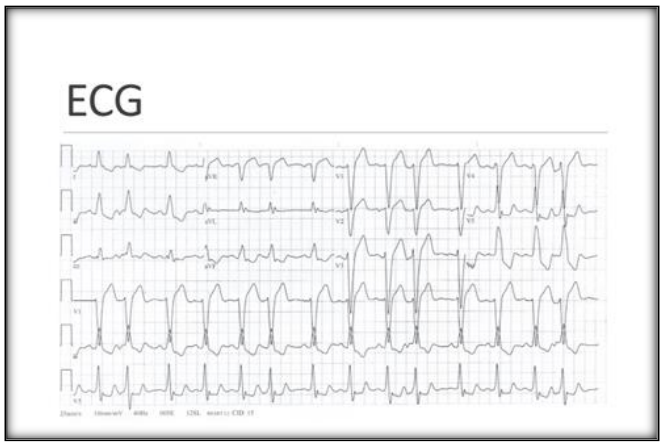
Patient was treated with anti-failure medications and digoxin. He further underwent CRT-D (Cardiac resynchronization therapy – defibrillator) implantation in 2012. Ultimately he succumbed to the disease and expired in the year 2015.

Case 2

Few months later, our first patient's elder sister presented to us with similar complaints. 46 year old female presented to us in 2016 with complaints of weakness of both lower limbs, progressive difficulty in standing and walking, and also getting up from squatting position. The above symptoms were of 4-5 months duration.

On examination- Alert, Fully conscious patient, oriented to time and place, hemodynamically Stable. Weakness of Proximal > Distal Muscles with a power of Grade 4-/5 in the proximal muscles (LL>UL) and 4+/5 in distal muscles without wasting. Ejection Systolic murmur at Pulmonary area on cardiac auscultation. No other specific signs.

Routine Investigations were normal. Creatine Kinase – 1212 (elevated). Thyroid Functions were normal. ECG revealed Complete LBBB (Figure 2). 2D ECHO was Normal, however subsequently patient developed complete heart block and presently patient is on PPI (Permanent Pace maker Implantation).



Case 3

Few months later our first patient's younger brother presented to us with similar complaints. 33 year old male presented to us with a history of progressive difficulty in walking. He also had difficulty in getting up from sitting and squatting position, difficulty in climbing stairs and walking uphill. The above symptoms were of 2 years duration.

On examination- Alert, Fully conscious patient, oriented to time and place. Hemodynamically Stable. Weakness of Proximal and Distal Muscles with a power of Grade 4/5 (LL>UL) without wasting. He had a waddling gait.

Routine Investigations were normal. Creatine Kinase – 1702 (elevated). Thyroid Functions were normal. ECG revealed Conduction abnormalities. 2D ECHO revealed Dilated Cardiomyopathy with asymmetrical septal hypertrophy. EMG – Myopathy with MYOTONIA. NCS was normal. DNA analysis: For mutation in DMPK (myotonic dystrophy protein kinase) gene and number of trinucleotide repeats (CTG) showed normal number of CTG repeats.

Muscle Biopsy was done. HPE: Sections from skeletal muscle tissue shows preserved architecture and focal increase in endomyseal fibrosis and adipose tissue infiltration. ATPase revealed atrophic type 1 and 2 fibres. Desmin immunolabelling shows subsarcolemmal and central aggregation in moderate numbers of fibres. Impression- Myofibrillar myopathy, the diagnosis of desmin related myopathy is considered.

Case 4

Going back to long past history of family, father of all these 3 children aged 60 years, presented in 1985 with proximal muscle weakness of upper limb and lower limb and distal muscle weakness of upper and lower limbs. Proximal muscle weakness was more than distal muscle weakness in both upper and lower limbs. His ECG was showing trifascicular block and he died in 1988. Mother was normal.

Table 1: Clinical and Investigative comparison of all cases

	Case 1	Case 2	Case 3	Case 4
Age of onset	42	46	33	60
Proximal muscle	Distal = proximal	Proximal > distal	Proximal= Distal	Proximal> distal

Distal muscle	Involved	Involved	Involved	Involved
Cardiac involvement	Present	Present	Present	Present
ECG	Trifascicular block with AF	Complete LBBB	First degree heart block	Trifascicular block
2D ECHO	Dilated cardiomyopathy	Normal	Dilated cardiomyopathy with asymmetrical septal hypertrophy	Not done

Discussion

Myofibrillar myopathy (MFM) encompasses a genetically and clinically heterogeneous group of inherited or sporadic skeletal muscle disorders characterized pathologically by the presence of myofibrillar dissolution associated with accumulation of myofibrillar degradation products. The term “myofibrillar myopathy (MFM)” was originally coined by Nakano et al to cover a variety of myopathies sharing a common finding of abnormal desmin accumulation.

Desmin is a protein that in humans is encoded by the DES gene. Desmin is a muscle-specific, type III intermediate filament that integrates the sarcolemma, Z disk, and nuclear membrane in sarcomeres and regulates sarcomere architecture. In the skeletal and cardiac muscles, normal desmin encircles the Z bands that hold together the actin filaments and help transmit tension along the myofibrils, protecting their structural integrity during repeated muscle contractures over time. Defects in the function of desmin, as well as in the other desmin-associated filaments, may therefore cause fragility of the myofibrils and impair contraction causing Cardiomyopathy and Skeletal Myopathy.

The true incidence of MFM is unknown. But a report published in the Brain – Journal of Neurology says ‘Desmin related myopathies are very rare diseases and as of 2004 only 60 patients have been diagnosed worldwide.’ Cardiomyopathy is present in 17% and is the leading cause of death among these patients. In our study all the four patients had cardiac involvement, 2 had cardiomyopathy, other 2 conduction block.

Autosomal dominant inheritance is common, however can be autosomal recessive or sporadic. Though children with recessive presentation of Desmin mutation do occur and in this presentation can be in early childhood. It is not always possible to determine the mode of inheritance in families because some mildly affected individuals remain undiagnosed.

Dominant genetic disorders occur when only a single copy of an abnormal gene is necessary to cause a particular disease. The abnormal gene can be inherited from either parent or can be a result of a new mutation in the affected individual. Approximately 25% of affected individuals have an affected parent. The risk of passing the abnormal gene from affected parent to offspring is 50% for each pregnancy. The risk is the same for males and females.[2]

The genes reaponsible for myofibrillar myopathies have been identifies in approximately 20% of affected individuals. These disorders have been categorized by the gene involved. The gene abnormality results in excess amounts of a particular proteinin muscle.[2]

Desminopathy – onset 20-30 years, DES gene/ desmin protein

Alpha- B crystallinopathy- onset 20-40 years, CRYAB gene/a-B crystalline protein

Myotilinopathy- Onset 27-77 years, Titin immunoglobin domain protein TTID gene/ Myotilin protein

Filaminopathy- oNst 37-57 years, FLNC gene/ filamin C protein

BAG3 related myofibrillar myopathy- Onst childhood, BCL-2 associated athanogene 3/ BG3 protein

Zaspopathy- Onset 44-73 years, LDB3 (ZASP) gene/ LIM domain binding protein 3. 2

Age of onset is 7 to 77 years (mean 54 years). Clinically it is characterized by slowly progressive weakness that can involve both proximal and distal muscles. Distal muscle weakness is present in about 80% of individuals and is more pronounced than proximal weakness in about 25% however only proximal muscle weakness is seen in 15-20% patients. In our study all the 4 patients had proximal involvement more than distal muscle involvement.

Other signs and symptoms of MFM can include an enlarged and weakened heart muscle (cardiomyopathy) and an abnormal heart rhythm(arrhythmia), muscle pain(myalgia) and loss of sensation and weakness in the limbs (peripheral neuropathy). For some people as the disease progresses, the muscles of the lungs may also be affected, which can result in repiratory failure. Individuals with this disease may have skeletal problems including joint stiffness (contractures). Rarely people with this disease can develop cataract.[1]

Creatine Kinase level – Can be elevated upto 7 times ULN, Electromyography, Nerve Conduction Studies, Muscle Biopsy - Histologic Analysis, Electron Microscopy, and Immunocytochemistry. Muscle biopsy is the ultimate which can clinch the diagnosis.

No specific treatment available. Symptomatic and treatment of complications. Pacemaker and implantable cardioverter defibrillator (ICD) -arrhythmia and/or cardiac conduction defects. Individuals with progressive or life-threatening cardiomyopathy are candidates for cardiac transplantation. Individuals with progressive or life-threatening

cardiomyopathy are candidates for cardiac transplantation. Respiratory support- consisting of continuous or bilevel positive airway pressure (CPAP and BIPAP)

Myofibrillar myopathy is a progressive muscle disease. In general MFM that first shows symptoms beginning in the childhood is more severe than the onset of symptoms in adulthood. Because MFM shows variable expressivity, the exact signs and symptoms for each person cannot be predicted, including whether or not an affected individual will have cardiomyopathy or respiratory failure. If Cardiomyopathy and respiratory failure are managed people with MFM are expected to have a normal life expectancy.[1]

Conclusion

Desmin related myopathies are very rare diseases and as of 2004 only 60 patients have been diagnosed worldwide. According to literature cardiomyopathy is present in 17% and is the leading cause of death among these patients. But in our study cardiac involvement is seen in all cases.

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