Lipid storage myopathy with clinical markers of Marfan syndrome: A rare association

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Abstract

Disorders of lipid metabolism can cause variable clinical presentations, often involving skeletal muscle, alone or together with other tissues. A 19-year-old boy presented with a 2-year history of muscle pain, cramps, exercise intolerance and progressive weakness of proximal lower limbs. Examination revealed skeletal markers of Marfan syndrome in the form of increased arm span compared with height, Kyphoscoliois, moderate pectus excavatum, high arched palate and wrist sign. He also had mild neck flexor weakness and proximal lower limb weakness with areflexia. Pathologic findings revealed lipid-laden fine vacuoles in the muscle fibers. Possibility of carnitine deficiency myopathy was considered and the patient was started on carnitine and Co Q. The patient made remarkable clinical improvement over the next 2 months. This case is reported for rarity of the association of clinical markers of Marfan syndrome and lipid storage myopathy and sparse literature on lipid storage myopathy in the Indian context.

Key Words

Carnitine deficiency myopathy, lipid storage myopathy, Marfan syndrome, muscle biopsy, neuromuscular diseases

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Introduction

Lipids are the main source of energy for muscle while at rest and during sustained exercise. There are four types of genetically diagnosable lipid storage myopathy (LSM): primary carnitine deficiency (PCD), multiple acyl-coenzyme A dehydrogenase deficiency (MADD), neutral lipid storage disease with ichthyosis (NLSDI) and neutral lipid storage disease with myopathy (NLSDM).[1] These four disorders usually show markedly increased lipid droplets in the muscle fibers. On the other hand, lipid storage could be mild or even absent in the defects of intramitochondrial fatty acid transport and beta oxidation.

Individuals with PCD show dramatic improvement with high-dose oral L-carnitine supplementation (100–400 mg/kg per day) and MADD due to electron-transferring-flavoprotein dehydrogenase mutations is riboflavin responsive 2010).[2-4]

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Carnitine plays an essential role in the transfer of long-chain fatty acids across the inner mitochondrial membrane. Carnitine deficiency syndromes include two primary types – systemic and muscle carnitine deficiency – and at least 15 syndromes in which carnitine deficiency seems to be secondary to genetic defects of intermediary metabolism or to other conditions.[5,6]

Diagnosis of Marfan syndrome, a connective tissue disorder, is challenging as it requires definition of diverse clinical features. The clinical diagnosis is made using the Ghent nosology, which unequivocally diagnoses or excludes Marfan syndrome in 86% of the cases[7]

Because of the age-dependent manifestations of the clinical symptoms, combined with the extreme heterogeneity of Marfan's syndrome, diagnosis in early childhood remains sometimes difficult.[8]

The association of LSM and markers of Marfan syndrome is not reported, and there is sparse literature on LSM in the Indian context.

Case Report

A 19-year-old boy, first born to second-degree consanguineous parentage, presented with fatigue, myalgia, pains and aches in the extremities, especially after sustained exercise, muscle cramps and progressive weakness of the proximal lower limbs

of 2 years duration, which was gradually worsening over the past 6 months. He had no history of wasting, twitching of muscles, hypertrophy of muscles, myoglobinuria, fluctuations or diurnal variations. There was no history of respiratory distress, bulbar weakness, cranial nerve disturbances, episodes of encephalopathy or cardiac symptoms. There was no family history of similar illness.

Examination revealed a young boy of thin and tall build with predominant skeletal markers of Marfan syndrome with arm span of 12 cm more than his height (arm span 182 cm, height 170 cm). He also had myopia, high arched palate, kyphoscoliosis [Figure 1a] and wrist sign positivity [Figure 1b] (tip of the thumb covering the entire fingernail of the fifth finger when wrapped around the contralateral wrist) and moderate pectus excavatum [Figure 1c]. He also had striae in skin over the back. He had neck flexor weakness, wasted small muscles of hands with proximal muscle weakness of both lower limbs and generalized areflexia, exaggerated lumbar lordosis and waddling gait. There was no ectopia lentis or cardiac or pulmonary involvement.

On evaluation, serum creatinine phosphokinase was mildly elevated (343 IU/L).Tandem mass spectroscopic analysis revealed normal levels of free and acylcarnitine species. Cardiac evaluation with ECG and ECHO were normal. There was no evidence of aortic root dilatation. Thyroid profile and serum lactate were normal. Nerve conduction study was normal. X-ray to rule out protrusio acetabulae and magnetic resonance imaging to look for dural ectasia was not done.

Left biceps muscle biopsy was subjected to hematoxilin eosin (HE) [Figure 2a], modified Gomori trichrome (MGT), periodic acid Schiff's (PAS), oil red O and a battery of enzyme histochemical stains (succinic dehydrogenase [SDH], nicotinamide adenine dinucleotide tetrazolium reductase [NADH-Tr], adenosine triphosphotase [ATPase, pH 9.5, 4.6, 4.3] and acid phosphatase). Morphologically, skeletal muscle tissue showed preserved architecture, normal endo and perimysial components and polygonal fibers with mild variation in diameter. Moderate numbers of myofibers in each of the fascicle showed multiple fine vacuoles giving a sieve-like appearance. These fibers were present in between normal-appearing fibers, giving a mosaic pattern. SDH and NADH-Tr revealed these fibers to be intensely stained and red granular (Ragged red) on MGT [Figure 2b]. The vacuoles were positive to oil red O and negative to PAS and acid phosphatase. Tiny pieces of skeletal muscle tissue fixed in 3% glutaraldehyde embedded in araldite for electron microscopy showed distortion of filamentous pattern, presence of lipid vacuoles and aggregates of mitochondria of varying sizes with altered mitochondrial cristae [Figure 3].

The patient was started on a low dose of carnitine and Co Q. His muscle pain decreased and his neck and proximal muscle weakness of lower limbs improved over the next 2 months. He fulfilled 5/7 of the systemic score in Ghent criteria of Marfan syndrome, although there was no family history of Marfan syndrome. In view of the lack of genetic analysis and family history, the patient does not fulfil Ghent criteria but the patient does have clinical markers of Marfan syndrome and needs close follow-up as evolution of more organ involvement is age dependent. Neck weakness in LSM is reported in one patient[9,10] and association with skeletal markers of Marfan is not reported in the literature.

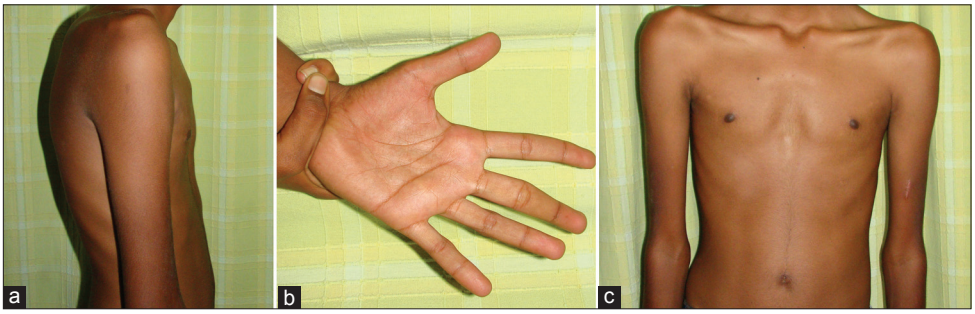

Figure 1: (a) Dorsolumbar kyphoscoliosis (b) Wrist sign (c) Pectus excavatum

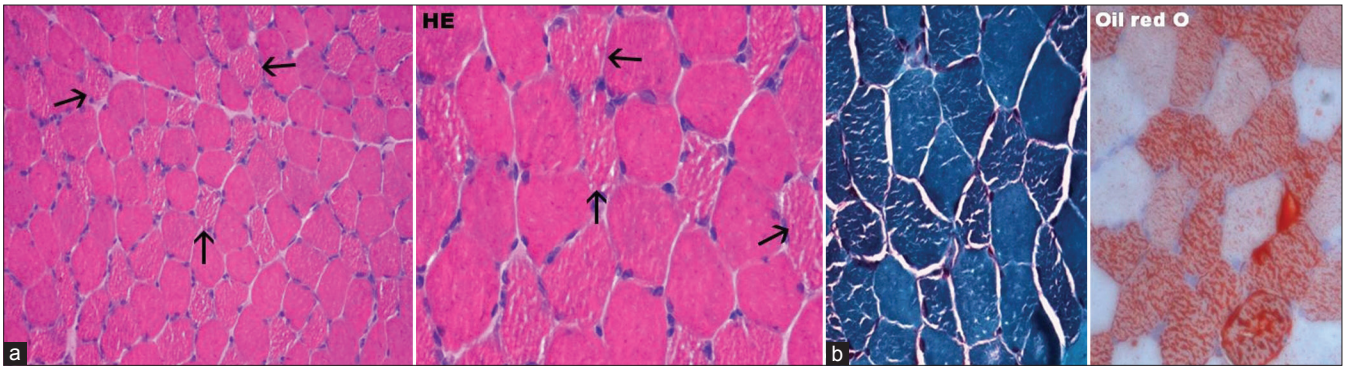

Figure 2: (a) Hematoxylin eosin stain – transversely cut skeletal muscle showing polygonal fibers. Note: Presence of multiple small vacuoles suggesting storage disorder (b) Lipid vacuoles ragged red in modified Gomori trichrome and positive oil red O stains

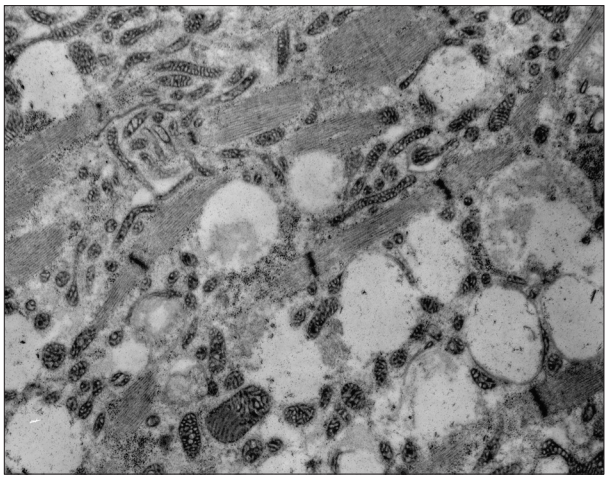

Figure 3: Electron microscopic graph showing fat vacuole and mitochondria with abnormal cristae ×5000

Discussion

LSM is relatively rare. A genetic epidemiologic study of the carnitine transporter gene OCTN2 from Japan estimates the incidence of primary systemic carnitine deficiency as one in 40,000 births. An NIH–National Library of Medicine, US-based database reports the prevalence of PCD in the general population to be one in 100,000 newborns. The incidence in Faroe islands is estimated to be one in 500 people. As per the Mayo clinic data (Minnesota newborn screening data), PCD has an incidence of approximately 1:21,000 live births.

The estimated frequency of MADD at birth ranges from one in 15,000 to one in 20,000 births in the US. Neutral lipid storage disorder prevalence is not known, and it is estimated to be <1/1,000,000. Around 50 cases have been reported in the medical literature.

The phenotype of lipid metabolism disorders is heterogeneous. The more severe variants present in infancy or childhood with primary involvement of liver or brain, whereas the milder adult forms are predominantly myopathic. Manifestations in infantile-onset patients are hypotonia, hypoketotic hypoglycemic encephalopathy, hepatomegaly and cardiomyopathy. In late-onset patients, constant or progressive muscle weakness associated with or without metabolic crisis is often seen in patients with LSM while recurrent rhabdomyolysis and myoglobinuria usually occur in patients with disorders affecting intramitochondrial fatty acid transport and b-oxidation.[3]

Deficiency of the OCTN2 carnitine transporter causes PCD, characterized by decreased carnitine accumulation in tissues. The manifestations are widely variable, ranging from asymptomatic cases, isolated cardiomyopathy to lethal metabolic decompensation. There is no clear correlation between genotype and either clinical or biochemical phenotype yet reported, and the wide phenotypic variability may be related to epigenetic or exogenous factors. Carnitine deficiency can manifest either as myopathic form when there is clinical weakness and muscle carnitine levels are low or as systemic form where there is muscle weakness and recurrent hepatic encephalopathy and carnitine in muscle, plasma and liver are decreased.[11]

Proper diagnosis often depends on determination of total carnitine in skeletal muscle or liver (or both).[6] Common blood tests may reveal increased levels of hepatic enzymes and Creatinine kinase. Extremely low levels of free carnitine and all acylcarnitine species are indicative of PCD. Carnitine transport study in fibroblasts may be used to confirm the diagnosis. On muscle pathology, markedly increased lipid droplets in both number and size in muscle fibers are seen, especially in type 1 fibers. Ultrastructural study often shows lipid droplets next to mitochondria, which are usually enlarged. Abnormal mitochondria of varying size with abnormal cristae configuration have been demonstrated.[12] Cytoplasmic bodies with dense core and radially arranged leptomeres and filaments were also demonstrated in some myofibres. As PCD is caused by the defect of OCTN2, searching for the mutations in *SLC22A5* is another way to establish the diagnosis of PCD.

Early carnitine therapy has been believed to prevent the occurrence of cardiomyopathy and other irreversible organ damage.[3]

Patients with neonatal onset of MADD present with hypotonia, hepatomegaly, nonketotic hypoglycaemia and metabolic acidosis and usually die early in infancy. Later onset patients manifest proximal myopathy with hepatomegaly and episodic metabolic crisis; these episodes can be lethal. Plasma-free carnitine level is decreased or normal. Concentrations of mainly medium- and long-chain acylcarnitines are elevated. Muscle biopsy shows features similar to those of PCD. Mutation analyses of *ETFA*, *ETFB* and *ETFDH* may be the most confirmative diagnostic method. Riboflavin supplement shows dramatic response.

NLSD present with ichthyosis, mild myopathy, hepatomegaly, ophthalmologic symptoms, neurosensory hearing loss, mental retardation and short stature. In NLSDI, the ichthyosis represents nonbullous congenital ichthyosiform erythroderma and the weakness is usually mild and predominant proximal. Cardiomyopathy is exclusively seen in almost half of the patients with NLSDM but not NLSDI, while neurosensory defects and mental retardation are commonly seen in NLSDI but not in NLSDM. The intracytoplasmic lipid storage in leukocytes (Jordan's anomaly) is visible on peripheral blood smear. In skeletal muscles, increased lipid droplets could be observed even in the presymptomatic period. Rimmed vacuoles in the muscles were reported in some NLSDM patients.[3]

Carnitine palmitoyl transferase II deficiency presents as recurrent attacks of myalgias, muscle stiffness or weakness with myoglobinuria. The attacks are prompted by prolonged exercise, prolonged fasting, high fat intake, exposure to cold, mild infection fever, emotional stress, general anesthesia or drugs. Neonatal onset may have dysmorphic features. Evaluation reveals elevated creatinine kinase and acylcarnitine levels. Enzymatic assay of leukocyte/fibroblast and mutation for CPT2 establishes diagnosis. Very long chain acyl-co enzyme A deficiency presents clinicopathologically similar to CPT II deficiency.

There is sparse literature on LSM in India.Five cases of carnitine myopathy were reported.[12] Three cases of LSM -two with myopathic form and one with pancreatitis,hepatic encephalopathy and myopathy were reported.[13]

Marfan syndrome is diagnosed by the revised US National Marfan Foundation 2010. Systemic score for diagnosis includes family history with presence of more than seven of the following features: wrist and/or thumb criteria, pectus carinatum deformity, pectus excavatum or chest asymmetry, plain flat foot, pneumothorax, dural ectasia, protrusio acetabulae, increased armspan to height, scoliosis or thoraco lumbar kyphosis, reduced elbow extension, facial features, skin striae, myopia and mitral valve prolapse.

In the absence of family history, systemic score more than 7 along with aortic root dilatation fulfils the criteria. Our patient fulfilled 5/7 features as elaborated earlier, although aortic root was not involved.

Diagnostic criteria is based on involvement of various systems like skeletal system,cardiovascular system,pulmonary system ,skin and integument along with genetic analysis or family history.[14]

Conclusion

LSM has varied clinical presentation. The diagnosis should be considered in young adults with muscle pain, fatigue and weakness with or without systemic features. Its association with Marfan syndrome has not been reported. Carnitine therapy in PCD shows dramatic clinical improvement, and it is potentially treatable.

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