

Editorial Commentary: Lipid Storage Myopathies

Limb-girdle syndromes are seen at all ages and include a wide variety of conditions. Classifying such syndromes can be challenging due to their slowly progressive nature, myriad etiologies ranging from genetic, inflammatory, metabolic, drug-induced and endocrinal diseases, and heterogeneous ways of clinical presentations. Storage myopathies, being uncommon and requiring special investigative workup, pose particular diagnostic difficulties. In this context, the manuscript in the current issue of *Annals of Indian Academy of Neurology*^[1]; “Mutation Spectrum of Primary Lipid Storage Myopathies” provides us with an in-depth analysis of this rare group of metabolic myopathies—the Lipid Storage Myopathies. There have been case reports from many parts of India about these uncommon diseases, but the current manuscript is the first case series from India, which provides detailed analysis and long follow-up of genetically confirmed cases of lipid storage myopathies from a neuromuscular center in south India.

Disorders of lipid metabolism can have a varied clinical presentation, often involving skeletal muscles in isolation or as part of a wider multisystemic illness. They present at different ages and have varied presentations ranging from exercise-induced myalgia, progressive limb-girdle syndrome, recurrent acute rhabdomyolysis, cranial neuropathies, and dropped head syndrome. Moreover, these patients tend to be near completely asymptomatic in between episodes with routine and specific investigations such as Creatinine phosphokinase (CPK) as well as tandem mass spectrometry results remaining normal as well as mass spectrometry also tend to remain normal. The diagnosis requires a high index of clinical suspicion supported by laboratory facilities to study the muscle biopsy, muscle metabolism, and genetic evaluation. In the past two decades advances have been made in phenotypic/genotypic presentations of the disease, new pathogenic mechanisms identified, and newer therapeutic molecules against specific genetic defects recognized, e.g., the late-onset riboflavin-responsive form of multiple acyl-CoA dehydrogenase deficiency.

Estimated prevalence of the most common type of lipid storage myopathy, Multiple acyl-coenzyme A dehydrogenase deficiency is 1 in 15,000 to 20,000 births in the United States, whereas the prevalence of carnitine palmitoyltransferase-2 and very-long-chain acyl-CoA dehydrogenase deficiency has been reported as 1 in 250,000 and 40,000 to 120,000, respectively.^[2] Neutral lipid storage myopathies are encountered frequently in China. Given the limitations of paucity of clinical neurologists and of the investigative facilities in India, the epidemiological aspects of lipid storage myopathies have yet to be worked out in the Indian context. Case series denoting profiles of lipid storage myopathies are few, given the overall rarity of the disease.^[3-8] and these discuss the clinical and investigative features of lipid storage myopathies. All studies do not include genetic

information. These studies have suggested that late-onset multiple acyl-CoA dehydrogenase deficiency (MADD) is the most common form of lipid storage myopathy, which is important to diagnose as patients respond favorably to riboflavin supplementation.^[5,6] There is a relative paucity of information as regards the neutral lipid storage myopathies and only 50 recorded cases in the literature exist so far.^[4] There have been cases of lipid storage myopathies not linked to any known genetic loci, an area that is open to further research.

In the current manuscript, the authors have presented a detailed review of the clinical and genetic profiles of 11 cases of lipid storage myopathies with special emphasis on the need for genetic confirmation in all suspected cases of lipid storage myopathies. The variability of the clinical profile is discussed. A point of note is the diagnostic delay of many years, underscoring the need for awareness of these conditions requiring a high index of suspicion and prompt intervention.

As facilities for genetic evaluation are becoming more available to our Indian patients, it is increasingly feasible to study the genotypes. This current manuscript demonstrates the important role that genetics has played in the confirmation of the suspected cases. Genetic analysis also provided novel pathogenic mutations in these groups of patients and the authors have discussed the basis of phenotypic variability in subgroups like cases of the dropped-head syndrome and the association with electron transport flavoprotein dehydrogenase mutation. Similarly, cases of bulbar involvement and cardiomyopathy were associated with flavin adenine dinucleotide synthase mutation. It needs to be borne in mind that the number of patients in the study is small to draw conclusions, understandably so, as the disease is uncommon.

Authors provide a nice perspective of the role and limitations of conventional testing such as CPK levels, magnetic resonance imaging (MRI) to display fatty infiltration and muscle edema, muscle biopsies to show vacuoles using special stains, and the use of tandem mass spectrometry in achieving such diagnoses. It is important to appreciate that none of these tests in isolation or in combination have 100% yield. CPK levels ranged from normal to up to 10-folds elevation and thus did not specifically help the diagnostic yield. MRI performed in four out of 11 patients demonstrated fatty changes in gluteus maximus; however, only two of these four had fatty changes in the anterior and posterior thigh and leg muscles. Similarly, muscle biopsy and tandem mass spectrometry showed abnormalities in about 50% of genetically proven cases.

The current manuscript also highlights many contrasting details as compared with the previously available information. Among five patients of electron transport flavoprotein

mutation, none had breathing difficulty in contrast to 78% of such patients from the Iranian study.^[9] In patients having carnitine palmitoyltransferase II mutation, tandem mass spectrometry was normal in all three as compared with a study in which all nine patients had abnormalities on (TMS).^[8] Although most of the patients carrying flavin adenine dinucleotide synthetase1 mutation had onset in infancy and majority succumbed to the illness in childhood; a solitary patient had late-onset in the third decade and had positive Beevor's sign and exaggerated deep tendon reflexes. These facts help awareness of the possible phenotypic variations from identical genetic mutations. A small sample size is one of the limitations of this excellent manuscript and a large multicentric study sampling various parts of India will go a long way in providing further information.

Clearly, to our knowledge, the current manuscript presenting the first such case series from India is important as it provides a detailed analysis of the spectrum of genetically proven lipid storage myopathies. Moreover, if identified early, these myopathies are potentially treatable causes of limb-girdle syndromes. Multicentric efforts will be required in the future to explain the nuances of clinical heterogeneity and phenotype-genotype correlation within this group of disorders.

Satish Khadilkar, Mehul Desai

Department of Neurology, Bombay Hospital Institute of Medical Sciences,
Mumbai, Maharashtra, India

Address for correspondence: Dr. Satish Khadilkar,
110, New Wing, First Floor, Bombay Hospital, 12 New Marine Lines,
Mumbai - 400 020, Maharashtra, India.
E-mail: khadilkarsatish@gmail.com

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