



Clinical and Pathological Features of Lipid Storage Myopathy; A Retrospective Study of a Large Group from Iran

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Abstract

Background: Lipid storage myopathies (LSMs) are rare diseases. The phenotype and genotype of lipid metabolism disorders are heterogeneous and divided into two major groups. Constant or progressive proximal and axial muscle weakness associated with or without metabolic crisis, is often seen in patients with LSM such as primary carnitine deficiency (PCD) or multiple acyl-coenzyme A dehydrogenase deficiency disorder (MADD). On the other hand, rhabdomyolysis triggered by fasting, fever, or physical activity usually occurs in patients with disorders affecting intramitochondrial fatty acid transport and β -oxidation, such as carnitine palmitoyltransferase II deficiency (CPT2), mitochondrial trifunctional protein deficiency and very-long-chain acyl-CoA dehydrogenase deficiency (VLCAD).

Methods: In this cross-sectional study, we summarized the clinical profiles and muscle histology of 64 Iranian patients diagnosed with LSM by muscle biopsy. These patients were selected from 3000 patients referred for muscle biopsy to Toos and Mofid children's hospitals during 2010 to 2016. Their affected siblings were also added to the study.

Result: In our study 45.3% of the patients were men and 54.7% were women. Mean age of the patients was 27.05 years (SD: 14.26) and the mean age of onset of symptoms in these patients was 20.94 (SD: 14.25) years. Most patients (70.3%) had proximal weakness and no bulbar involvement. Only 9.3% of the patients had a positive family history.

Conclusion: LSMs are not uncommon in Iran and their phenotype can mimic inflammatory myopathy or limb girdle muscular dystrophy. Overall the demographic and clinical features of LSMs in Iranian patients were similar to prior reports.

Keyword: Lipid storage myopathy; Iran; Muscle biopsy; Clinical

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Introduction

Lipid myopathies (LMs) are a multi-systemic heterogeneous group of lipid metabolism disorders caused by defects in oxidation of fatty acids and divided into two groups. Muscle symptoms could fluctuate or be stable. Constant or progressive proximal and axial muscle weakness associated with or without metabolic crisis, is often seen in patients with lipid storage myopathy (LSM) such as primary carnitine deficiency (PCD) or multiple acyl-coenzyme A dehydrogenase deficiency disorder (MADD), while rhabdomyolysis triggered by fasting,

fever, or physical activity usually occurs in the patients with disorders affecting intramitochondrial fatty acid transport and β -oxidation, such as carnitine palmitoyltransferase II deficiency (CPT2), mitochondrial trifunctional protein deficiency and very-long-chain acyl-CoA dehydrogenase deficiency (VLCAD). The most common types of LSMs are MADD, PCD, and neutral lipid storage disease (NLSD) with or without ichthyosis. They are readily diagnosed by muscle biopsy with vacuolar myopathy appearance and positive oil red O or Sudan black stains. Under the electron microscope, the lipid droplets seem empty

without a limiting membrane. They are lying between the myofibrils and in subsarcolemmal spaces, often adjacent to the mitochondria. But lipid droplets could be little or even not identified in muscle biopsy of the patients with the defects of fatty acid transport and β -oxidation. Fatty acids are not used to initiate activity but are used after 20-30 minutes and are the main energy source for muscles after one hour. Hence during long-term activities-and in resting state lipids would develop energy for muscles. So it is rational that lipid metabolism disorders occur after long-term activities and/or fasting.¹⁻⁷

This study would help developing a pathological and clinical information database according to the geographical distribution based on the diagnosis of LSM on muscle biopsies to prepare possible and appropriate treatment opportunities.

Materials and Methods

This was a cross-sectional study. These patients were selected from 3000 muscle biopsy reports from Toos and Mofid children's hospitals during 2010-2016. Their affected siblings were also added to the study. Sixty-four patients were studied. The pathological and clinical information of the patients were extracted from existing medical reports.

Data were analyzed using SPSS software, version 22. Chi-square, Fisher's exact, and *t* tests were used as appropriated.

Results

In our study, there were 29 (45.3%) men and 35 (54.7%) women. The mean age of the patients was 27.05 (SD: 14.26). The youngest patient was 2 years and the oldest one was 63 years old. The mean duration between diagnosis and onset of symptoms was three years and nine months with median of 1 year (range from 2 months to 18 years). The mean age at onset of symptoms was 20.94 years (SD: 14.25). The youngest patient had symptoms since birth and the latest age of onset of symptoms was 62 years.

Most patients (70.3%) had proximal weakness. 3.1% had distal weakness and the other 26.6% had generalized weakness without any statistically significant difference between the men and women ($P = 0.974$). 10.9% of the patients had bulbar involvement without any significant difference between men and women ($P = 0.489$).

15 (23%) patients had positive family history in first degree relatives and 6 (9.3%) had positive family history in second degree relatives and most of the parents had no familial relationships. The most common site of muscle biopsies (0.35%) was biceps muscle. The rest were taken from deltoid, vastus lateralis, quadriceps, anterior tibialis, and gastrocnemius muscles.

In our study the common histopathological findings were diversity in size of fibers and round or angular atrophic fibers. Many fibers had multiple clear round

cytoplasmic or sub-sarcolemmal vacuoles in various sizes that were mainly small (Figure 1a). These vacuoles were almost all labelled with Oil-red-O stain (Figure 1b). Necrotic fibers were seen in only two (3.1%) and myophagocytosis and nuclear clumps were present in 7 (10%) and one (1.5%) patient, respectively. Endomysial connective tissue did not increase in any patient. There was no fiber type grouping, no inflammation and no adipose tissue replacement. In the NSLD subtype, red rimmed vacuoles were seen in the muscle biopsies of two (3.1%) patients (figure 1c), of which one had ichthyosis.

Discussion

LSM is rare with an incidence rate of 1/40 000 births for primary systemic carnitine deficiency in Japan. This rate

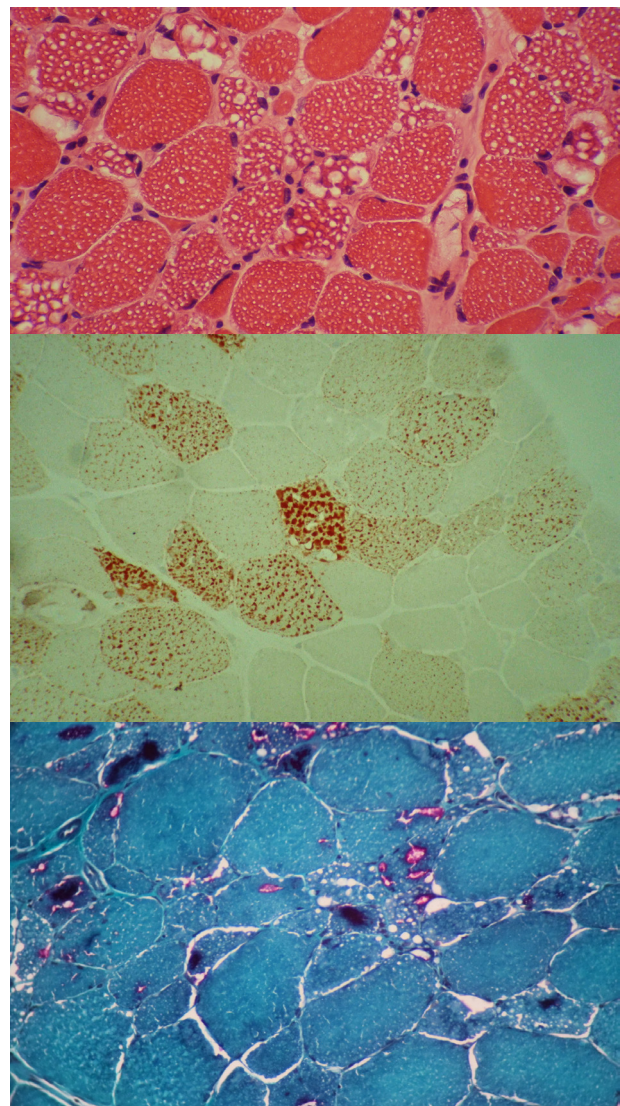


Figure 1. (a) Vacuolar myopathy with numerous cytoplasmic vacuoles (Hematoxylin and eosin $\times 400$). (b) Almost all cytoplasmic vacuoles are stained (Oil-red-O $\times 400$). (c) Red-rimmed vacuoles are seen accompanied by clear cytoplasmic vacuoles (modified Gomori Trichrome $\times 400$).

is 1/100 000 births in the United States and 1/500 births in Faeroe Island. The birth prevalence rate of PCD is 1/ 21 000 births in Minnesota.^{8,9} The prevalence rate of MADD is 1/15 000 births to 1/20 000 births in United States. It seems that MADD is the most common type of LSM in Iran.⁴ Neutral LSMs are less assessed and probably 1/one million births with 50 reported cases¹⁰

The phenotype of LSM is heterogeneous, and in childhood, brain and liver involvement are more prominent. Adulthood onset forms are less severe with muscle involvement. Infantile presentations are hypotonia, hypoglycemic hypoketotic, encephalopathy, hepatomegaly, and cardiomyopathy. The initiation symptoms in adults are more insidious with or without metabolic crisis.¹¹ Few studies have been reported from India. Five cases of carnitine deficiency myopathy were reported of which three were LSM, and one had pancreatitis, and one had hepatic encephalopathy.^{12,13}

All our patients had muscle weakness, most of which (70%) were proximal and 3.1% were distal and the others were generalized. Ohkuma and colleagues reported a 55% weakness rate which was mainly proximal or generalized.¹⁴ We found that 10.9% of the patients had bulbar involvement. Another study assessed 9639 muscle biopsies and LSM in 47 (0.5%) biopsies. They reported no sex difference similar to our study. The age of onset was 37-75 years and 8 out of 47 patients had a positive family history.¹⁴

Early MADD is characterized with hypotonia, hepatomegaly, non-hypoketotic hypoglycemia, and metabolic acidosis with early neonatal death. The late onset type presents with proximal myopathy. The free carnitine level is normal or reduced but acylcarnitine with medium to long chain is increased. Muscle biopsies are similar to PCD. Final diagnosis is with ETFB, ETFA, and ETFDH gene studies. Therapeutic response to riboflavin is dramatic.⁴ NLSD could present with ichthyosis, mild myopathy, hepatomegaly, visual symptoms, sensorineural hearing loss, short stature, and mental retardation. Ichthyosis is usually seen as nonbullous congenital ichthyosiform erythroderma. Cardiomyopathy is seen in NLSD with ichthyosis but sensorineural disorder and mental retardation are more common in NLSD without ichthyosis. In Jordan anomaly fat deposition in leukocytes could be seen even in pre-clinical state. Patients with NLSD occasionally have rimmed vacuoles in muscles.¹⁵ Carnitine deficiency may present as myopathy with decreased muscle carnitine. The systemic form has muscle weakness and recurrent hepatic encephalopathy with decreased carnitine in the muscle, plasma, and liver.^{16,17} The hepatic enzymes and CPK are raised. Severe decrease of free carnitine and acylcarnitine are seen in PCD.¹²

Also 4.7% of the patients had a positive family history and 95.3% did not. Ohkuma et al also reported similar results.¹⁴ We found that 11 (17.2%) patients had parents

who were first degree relatives and 5 (7.8%) were second degree relatives.

Conclusion

The results of our study showed that LSMs are not uncommon in Iran and overall demographic and clinical feature of LSMs in Iranian patients is similar to prior reports. Proximal weakness is seen in most patients, so phenotype of these patients mimics limb girdle muscular dystrophies or inflammatory myopathies. Positive family history and having first degree relative status in parents were not seen frequently. We found that sex and clinical presentation had no association with the disease. However, further studies with larger sample size, and reporting the results of genetic evaluation are recommended to attain more definite results.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

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Ethical Statement

The study was performed according to the principles of the Declaration of Ethical Committee of Shahid Beheshti University of Medical Sciences (ethical code: IR.SBMU.RETECH.REC.1396.252).

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