Int J Clin Exp Pathol 2020;13(3):559-562
www.ijcep.com /ISSN:1936-2625/IJCEP0105754

Case Report

Neutral lipid storage disease with myopathy presenting asymmetrical muscle weakness: a case report

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Received December 1, 2019; Accepted January 19, 2020; Epub March 1, 2020; Published March 15, 2020

Abstract: NLSDM is a rare metabolic myopathy caused by mutations in the patatin-like phosphatase domain protein 2 (PAPLA2) genes. In the present study, we describe the clinical and genetic findings in our Chinese patient with NLSDM. Sequence analysis of PNPLA2 gene was performed. Gene analysis for PNPLA2 revealed an identical homozygous mutation c.757+1G>T in our patient. The clinical symptoms of our patient are related to the type of mutation in the PNPLA2 gene and environmental effects.

Keywords: ATGL, myopathy, gene mutation, NLSDM, PNPLA2

Introduction

Neutral lipid storage disease with myopathy is a rare disease characterized with accumulation of triglyceride. Neutral lipid storage disease with myopathy (NLSDM) and neutral lipid storage disease with ichthyosis (NLSDI) is divided according to the pathogenic genes and clinical feature. NLSDM is an autosomal recessive disease caused by mutations in the patatin-like phosphatase domain protein 2 (PAPLA2) gene. Most patients with NLSDM often present in adulthood (median age is 30 years), between the second or third decade, with a progressive muscle weakness involving both proximal and distal limb muscle, about 69% of which is mainly proximal, and the distal weakness can be involved in the later period [1]. A case of NLSDM with asymmetrical muscle weakness was reported to improve clinicians' awareness of the disease.

Patient

This 33-year-old woman was born in Guizhou, China. She presented at the age of 27 years with a subacute upper limbs weakness. As time progressed, she began to complain of lower limb weakness at the age of 31 years. Her family history did not share the same symptoms. The weakness of the right upper limb was more severe than that of the left upper limb; and the weakness of the proximal lower limbs was more severe than that of the distal. There was no muscle atrophy (**Figure 1**). Serum CK was elevated to 2171.4 U/L; triglyceride (TG) was 2.4 mmol/L. The abdominal ultrasound was not obviously abnormal. The cardiac ultrasound showed mild tricuspid regurgitation. The normal electrocardiogram showed normal electrocardiograms. The MRI of bilateral thigh nuclear showed no obvious abnormalities. Electromyographic diagrams showed myogenic damage. Muscle biopsies revealed the proliferation of connective tissue and adipose tissue in muscle bundles in HE and MGT staining. The muscle fibers in the muscle bundle were arranged closely and varied in size. Most of the muscle fibers showed more fine vacuoles, and some of them fused to form fissures or vacuoles (**Figure 2**). Genetic analysis revealed a homozygous splicing mutation in exon 6 of PNPLA2 gene, c.757+1G>T. The patient was diagnosed with NLSDM.

Discussion

NLSDM is a rare genetic metabolic disease caused by a mutation in the PNPLA2 gene that prevents the hydrolysis of triglycerides (TG).

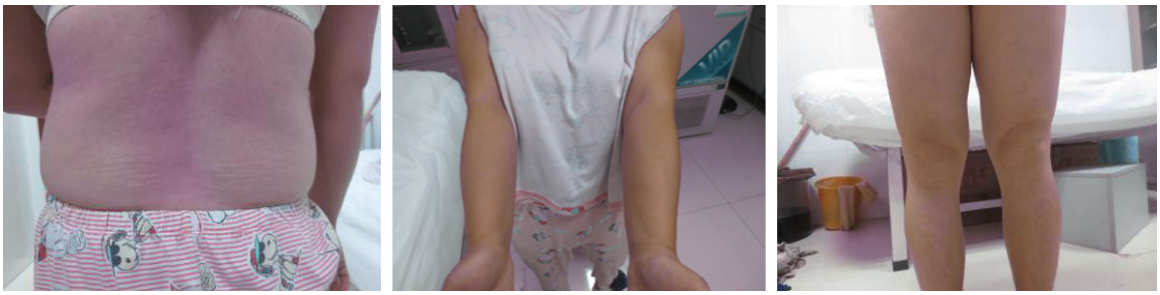

Figure 1. Right upper limb and proximal lower limbs weakness, not any limb or axial muscle atrophy.

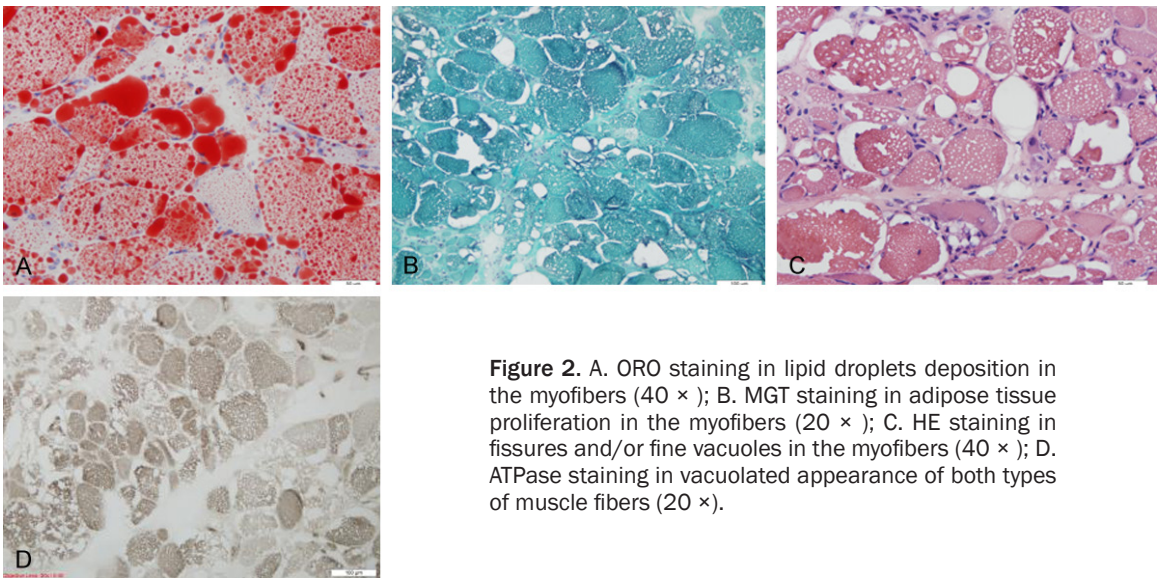

Figure 2. A. ORO staining in lipid droplets deposition in the myofibers (40 ×); B. MGT staining in adipose tissue proliferation in the myofibers (20 ×); C. HE staining in fissures and/or fine vacuoles in the myofibers (40 ×); D. ATPase staining in vacuolated appearance of both types of muscle fibers (20 ×).

The PNPLA2 gene encodes adipose triglyceride lipase (ATGL), which is the rate-limiting enzyme and catalyzes the initial step in the hydrolysis of triglycerides. ATGL releases long-chain fatty acids (LCFA) as the main energy source through intracellular TG hydrolysis, generating energy [2, 3]. Most of the mutations in the PNPLA2 gene cause a breakdown of triglycerides and lead to TG accumulation in various organs and tissues such as skeletal muscle, heart muscle, liver, and pancreas [4-6].

Different tissues involved in the course of the disease will lead to different diseases, with greater clinical heterogeneity, from mild symptoms to more severe conditions. Triglycerides are deposited in skeletal muscle, leading to limb weakness. This is also the predominant clinical feature of NLSDM. The weakness of the proximal limb can be involved in the early stage, as time progresses, the distal limb can be affected. In addition to the manifestation of limb weakness, NLSDM patients often have accompanying non-specific symptoms such as cardiomyopathy, hyperlipidemia, diabetes, and pancreatitis. Studies have found that the type of mutation in the PNPLA2 gene affects the lipolytic activity of ATGL, leading to different clinical symptoms. Nonsense mutations will cause translation to terminate prematurely, proteins cannot be synthesized, and lipolytic activity will be lost, which will cause significant cardiac dysfunction, while other mutation types may cause the production of a shorter ATGL protein, and reduce lipolytic activity. A low amount of lipolytic activity may preserve cardiac function and does not cause serious heart dysfunction [7]. In this case, with the exception of skeletal muscle involvement, other systems are not significantly affected. NLSDM genotype is closely related to clinical manifestations. According to reports, nearly 20% of NLSDM female patients and 55% of male patients have cardiac damage [5]. Cardiac abnormalities of

patients often appear in the late course of the disease, so in order to improve the accuracy and speed of early diagnosis, it is necessary to improve the correlation between genotype and phenotype.

In laboratory tests, a great significant diagnosis of NLSDM can be easily performed through the detection of lipid vacuoles in peripheral blood leucocytes, also known as Jordans' anomaly. In blood biochemical examination, the serum CK of NLSDM patients will have a sustained mild to moderate increase. The increase of the CK may have occurred before the patient's onset, indicating that the patient had a subclinical period before the clinical symptoms appeared [8]. It can pay the clinician's attention to asymptomatic elevated CK value, and then improve the diagnosis speed of NLSDM.

Biopsy of skeletal muscle tissue, a large amount of lipid droplet deposition can be seen through pathological analysis of muscle fibers, which is a pathological feature of neutral lipid storage disease, but the pathology lacks the diagnostic characteristics of neutral lipid storage disease typing. It has been reported that rimmed vacuoles are found to separate NLSDM from other neutral lipid storage disease, but further analysis of the gene lineage of neutral lipid storage disease is needed to make a clear typing diagnosis [9, 10].

The homozygous splicing mutation of the PNPLA2 gene c.757+1G>T found in this patient has been reported as a pathogenic mutation. This case was reported as the fourth report. The seven reported NLSDM patients were all PNPLA2 gene c.757+1G>T homozygous splicing mutations, including this patient, despite having the same PNPLA2 gene mutation (c.757 1G>T), but NLSDM patients still show clinical heterogeneity, indicating that the phenotype may not be seriously affected by genetics. There are many environmental risk factors in the development of NLSDM [6, 11, 12].

Thus far, the total number of NLSDM patients found is about 50. Due to the rarity of the disease and the variety of phenotypes, the results of laboratory tests, electrophysiological tests, and imaging tests are not specific, which undoubtedly increases the difficulty of diagnosis. Muscle tissue biopsy has a certain specificity for the diagnosis of NLSDM. Genetic testing is the gold standard for diagnosis of NLSDM. Through genetic testing, less than 20 mutation sites of PAPLA2 gene have been found in China. NLSDM patients with different mutation sites have different clinical manifestations, and patients with the same mutation site also have different clinical manifestations. Therefore, while improving the genotype-phenotype correlation, we must also pay attention to the different performance affected by disease course and environmental effects. Due to the rarity and stealthiness of the disease, this case report has increased the number of NLSDM patients and provided cases for the study of NLSDM.

NLSDM currently lacks specific treatment. This patient has been treated with hormones but has not improved significantly. Recent studies on triglyceride metabolism have shown that beta-activators may be useful in the treatment of NLSDM. Beta-adrenergic agonists may inhibit the expression of GOS2 protein (ATGL inhibitory protein), improve ATGL protein synthesis, and thereby increase the enzymatic activity of ATGL [13]. Improving the genotype-phenotype correlation, should thereby improve the prognosis of NLSDM and enable personalized treatment.

Disclosure of conflict of interest

None.

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