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Case report

Distal lipid storage myopathy due to *PNPLA2* mutation

Aya Ohkuma [a,b,c], Ikuya Nonaka [a], May Christine V. Malicdan [a], Satoru Noguchi [a], Satoru Ohji [b], Kyoichi Nomura [b], Hideo Sugie [d], Yukiko K. Hayashi [a], Ichizo Nishino [a,*]

[a] *Department of Neuromuscular Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry (NCNP), 4-1-1 Ogawahigashi-cho, Kodaira, Tokyo 187-8502, Japan*

[b] *Department of Neurology, Saitama Medical Center, Saitama, Japan*

[c] *Department of Neurology, Saitama Medical University, Saitama, Japan*

[d] *Jichi Children's Medical Center Tochigi, Jichi Medical University, Tochigi, Japan*

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Abstract

Distal myopathy is a group of heterogeneous disorders affecting predominantly distal muscles usually appearing from young to late adulthood with very rare cardiac complications. We report a 27-year-old man characterized clinically by distal myopathy and dilated cardiomyopathy, pathologically by lipid storage, and genetically by a *PNPLA2* mutation. The patient developed weakness in his lower legs and fingers at age 20 years. Physical examination at age 27 years revealed muscle weakness and atrophy predominantly in lower legs and hands, and severe dilated cardiomyopathy. The patient had a homozygous four-base duplication (c.475_478dupCTCC) in exon 4 of *PNPLA2*.

Keywords: Distal myopathy; Lipid storage myopathy; Neutral lipid storage disease with myopathy; *PNPLA2*

1. Introduction

Lipid storage myopathy (LSM) is a pathologically defined entity with accumulation of triglycerides in the muscle fiber. Six causative genes for only four diseases have been identified: *SLC22A5* for primary carnitine deficiency (PCD); *ETFA*, *ETFB*, and *ETFDH* for multiple acyl-CoA dehydrogenase deficiency (MADD); *ABHD5* for neutral lipid storage disease with ichthyosis or Chanarin–Dorfman syndrome; and *PNPLA2* for neutral lipid storage disease with myopathy (NLSDM) [1–3].

PNPLA2 encodes an adipose triglyceride lipase; mutations in this gene were recently reported in three patients who presented with LSM and variable cardiac involvement [1]. Here, we report a Japanese patient with a *PNPLA2* mutation presenting with distal myopathy and severe dilated cardiomyopathy and showing numerous rimmed vacuoles on muscle pathology.

2. Case report

A 27-year-old man had slowly progressive muscle weakness. Despite being a slow runner since childhood, he belonged to a mountaineering club and had no difficultly climbing mountains. At 20 years, he noticed difficulty climbing down the stairs, and gradually developed distal dominant muscle weakness and atrophy. Family history was non-contributory.

Upon consultation with us at 27 years, he had marked muscle weakness and atrophy in the extremities predominantly in the lower legs (Fig. 1A) and fingers (Fig. 1B). Examination of the muscle strength showed 3–4/5 asymmetric weakness over the deltoid, biceps brachii, extensor digitorum, gastrocnemius, and tibialis anterior. Grasping power was 12 kg on right and 10 kg on left (normal

* Corresponding author. Tel.: +81 42 346 1712; fax: +81 42 346 1742.
E-mail address: nishino@ncnp.go.jp (I. Nishino).

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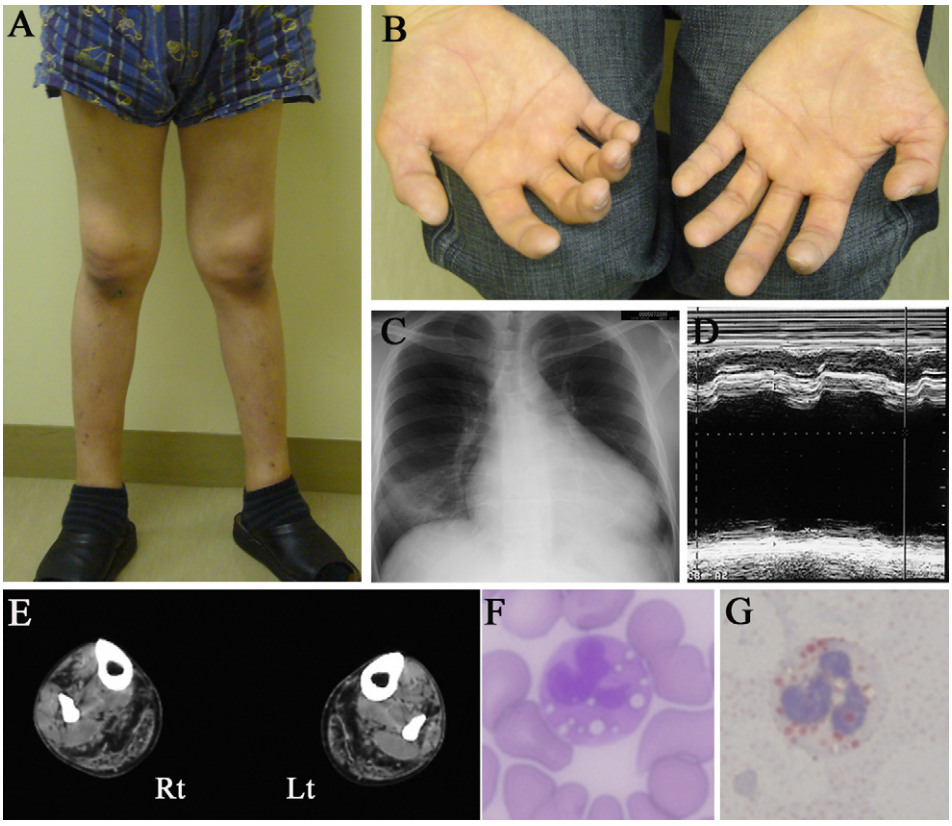

Fig. 1. The patient had distal muscle atrophy especially in the lower legs (A) and thenar muscles (B). Chest X-ray showed cardiomegaly with cardiothoratic ratio of 63% (normal cardiothoratic ratio <50%) (C). Echocardiogram showed left ventricular enlargement with decreased ejection fraction of 18% (normal >60%) (D). Calf muscles were involved relatively sparing tibialis anterior on CT (E). Note many vacuoles of leukocyte by Wright–Giemsa (F), which are positively stained by oil red O (G).

values = 43–56 kg). Deep tendon reflexes were absent. No skin abnormality was seen. Chest X-ray revealed cardiomegaly (Fig. 1C). Echocardiogram showed left ventricular enlargement with decreased left ventricular ejection fraction of 18% (normal >60%), left ventricular end-diastolic dimension of 78 mm, left ventricular end-systolic dimension of 70 mm, interventricular septum thickness of 8 mm and posterior wall thickness of 8 mm (Fig. 1D). ECG showed negative Q wave in lead I, negative P wave in V_1 and occasional ventricular extra-systoles. EMG showed myopathic changes. His respiratory function was normal. Serum creatine kinase was elevated (412–1697 IU/L; normal value <170). Serum cholesterol, TG, LDL-cholesterol and glucose were within normal ranges. In leukocytes, Jordans anomaly [4], multiple tiny vacuoles due to lipid accumulation, was seen (Fig. 1F and G). Muscle CT showed decreased densities in both soleus, both gastrocnemius, and right tibialis anterior muscles (Fig. 1E).

Muscle biopsy from the left biceps brachii muscle revealed marked variation in fiber size. Numerous lipid droplets were seen in virtually all type one fibers (Fig. 2A). In addition, rimmed vacuoles were observed in scattered fibers (Fig. 2B). Dystrophin, caveolin-3, and dysferlin immunohistochemistry were normal. On electron microscopy, markedly increased lipid droplets were seen between myofibrils where mitochondria appeared pyknotic (Fig. 3A). Numerous autophagic vacuoles were also observed (Fig. 3B). Total and free muscle carnitine levels were 13.2 and 3.9 nmol/mg non-collagen protein, respectively (reference: total, 15.7 ± 2.8; free, 12.9 ± 3.7).

We sequenced all exons and the flanking intronic regions of all six known causative genes for LSM in genomic DNA. In the patient, we identified a homozygous four-base duplication (c.475_478dupCTCC) in exon 4 of *PNPLA2* (Gene ID: 57104), predicted to result in a premature stop codon at amino acid position 178. Heterozygous c.475_478dupCTCC mutation was confirmed in both healthy parents. We did not find any sequence variant in other candidate genes, including *GNE* gene.

3. Discussion

The patient presented has been followed up with a tentative diagnosis of distal myopathy. In fact, one patient in the first report of *PNPLA2* mutations had distal dominant muscle weakness although the other two had proximal muscle involvement [1]. Therefore, distal myopathy may not be uncommon in LSM associated with *PNPLA2* mutations.