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Case report

Sporadic centronuclear myopathy with muscle pseudohypertrophy, neutropenia, and necklace fibers due to a *DNM2* mutation

Teerin Liewluck [a,*], Tracy L. Lovell [b], Anna V. Bite [a], Andrew G. Engel [a]

[a] Department of Neurology and Muscle Research Laboratory, Mayo Clinic College of Medicine, Rochester, MN, USA
[b] Northeast Georgia Diagnostic Clinic, Gainesville, GA, USA

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ABSTRACT

Dynamin 2 gene (*DNM2*) mutations result in an autosomal dominant centronuclear myopathy (CNM) and a Charcot-Marie-Tooth (CMT) neuropathy. *DNM2*-CMT but not *DNM2*-CNM patients were noted to have neutropenia. We here report a man with paravertebral muscles hypertrophy and mild neutropenia. His muscle biopsy was typical for CNM with additional "necklace" fibers. Sequencing of *DNM2* revealed a known heterozygous c.1269C > T (p.Arg369Trp) mutation. Necklace fibers were considered as a pathological hallmark of late onset X-linked CNM due to mutations in *MTM1* but have not been observed in *DNM2*-CNM. The findings broaden the features of *DNM2*-myopathy.

1. Introduction

Centronuclear myopathies (CNM) are genetically heterogeneous congenital myopathies with the common pathological feature of numerous myofibers containing centrally-placed nuclei without significant muscle fiber necrosis or regeneration [1]. Mutations in the myotubularin (*MTM1*) [2], the amphyphisin 2 (*BIN1*) [3], and the dynamin 2 (*DNM2*) [4] genes cause X-linked, autosomal recessive, and autosomal dominant forms of CNM, respectively. A mutation in the skeletal muscle ryanodine receptor (*RYR1*) was reported in one CNM patient [5]. Interestingly, myotubularin, amphyphisin 2, and dynamin 2 are essential for clathrin-mediated endocytosis and their defects cause similar morphologic changes [6,7]. However, the necklace fibers were considered a specific marker for late-onset *MTM1*-related CNM [8].

Dynamin 2, a ubiquitously expressed 100-kDa GTPase, plays a role in vesicle endocytosis and centrosome organization [4]. It is composed of five domains including a N-terminal GTPase domain, a middle domain, a pleckstrin homology domain, a GTPase effector domain, and a C-terminal proline-rich domain [4]. *DNM2* mutations give rise to autosomal dominant CNM and Charcot-Marie-Tooth (CMT) neuropathy with intermediate or normal nerve conduction velocities [4,9,10]. To date, all *DNM2* mutations causing myopathy occurred in the middle domain, the C-terminal of the pleckstrin homology domain, or the GTPase effector domain [11]. Patients carrying mutations in the C-terminal of the pleckstrin homology domain have an unusual perinatal onset [12]. In contrast, most mutations in *DNM2*-CMT occur in the N-terminal of the pleckstrin homology domain with only single mutations in the middle and the proline-rich domains [9].

Both *DNM2*-myopathy and *DNM2*-CMT patients have distal limb muscle weakness. Involvement of ocular and eyelid elevator muscles has been noted in *DNM2*-CNM and less often in *DNM2*-CMT [9,13]. A minority of *DNM2*-myopathy patients has a mild axonal neuropathy, but none of *DNM2*-CMT patients have a myopathy by electrophysiologic and pathologic criteria [13–15]. *DNM2*-CMT patients may also have neutropenia and cataracts, but no *DNM2*-CNM patients have neutropenia and only one *DNM2*-CNM patient had cataracts [9,16].

We report a patient with paravertebral muscle pseudohypertrophy, mild neutropenia, and necklace fibers due to a known heterozygous mutation affecting the middle domain of dynamin 2.

2. Case report

2.1. Patient

A 21-year-old man presented at the emergency room with acute abdominal pain, nausea, and mild epigastric tenderness. He

* Corresponding author. Address: Department of Neurology and Muscle Research Laboratory, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA. Tel.: +1 507 284 5102; fax: +1 507 284 5831.
E-mail address: liewluck.teerin@mayo.edu (T. Liewluck).

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had mild neutropenia with an absolute neutrophil count of 1900 cells/μl (normal 2200–4800 cells/μl). Other routine blood tests as well as serum amylase and lipase levels were normal. CT scan of the abdomen showed no intra-abdominal abnormality but revealed an increase in size and fatty replacement of the thoracolumbar paravertebral and anterior abdominal muscles (Fig. 1A). The abdominal pain resolved after administration of analgesic and antiemetic agents.

Retrospectively, the patient was born at full term with no perinatal complications. His motor development was normal. He kept up with his peers in physical activities during his childhood, and has noted no muscle weakness or sensory symptoms. No other family members were similarly affected. There was no spinal deformity and spine mobility was unrestricted. Except for hypertrophy of the paraspinal muscle (Fig. 1B), his examination was normal. The serum CK level was 364 U/L (normal 24–195 U/L). The blood thyrotrophin level was normal. The mild neutropenia had been noted 3 years ago; there was no history of severe or recurrent infections. No electrodiagnostic studies were performed.

2.2. Muscle biopsy

A biopsy of the rectus abdominis muscle showed the muscle fiber diameters to vary from 30 to 90 μm, with a moderate to marked increase in perimysial fatty and a mild increase in endomysial fibrous connective tissue. Ninety-four percents of the muscle fibers harbored one or more centrally-placed nuclei (Fig. 1C). A single necrotic fiber was observed. Regenerating fibers were absent. In oxidative enzyme-reacted sections, myofibers with central nuclei showed a radial arrangement of the myofibrils, and scattered fibers displayed peripheral accentuation of enzyme activity in a necklace pattern (Fig. 1D). Each necklace fiber harbored a single central nucleus. Muscle fibers in PAS and myophosphorylase-reacted sections also showed a necklace-like accentuation. Twelve percents of myofibers in myophosphorylase-reacted section and eight percents of myofibers in NADH dehydrogenase-reacted section were necklace fibers. As adjudged by ATPase-reacted sections, type 1 fibers were more abundant and had a smaller mean diameter than type 2 fibers. Sarcoplasmic/Endoplasmic reticulum calcium ATPase 2 (NCL-SERCA2, 1:200, Novocastra), dihydropyridine

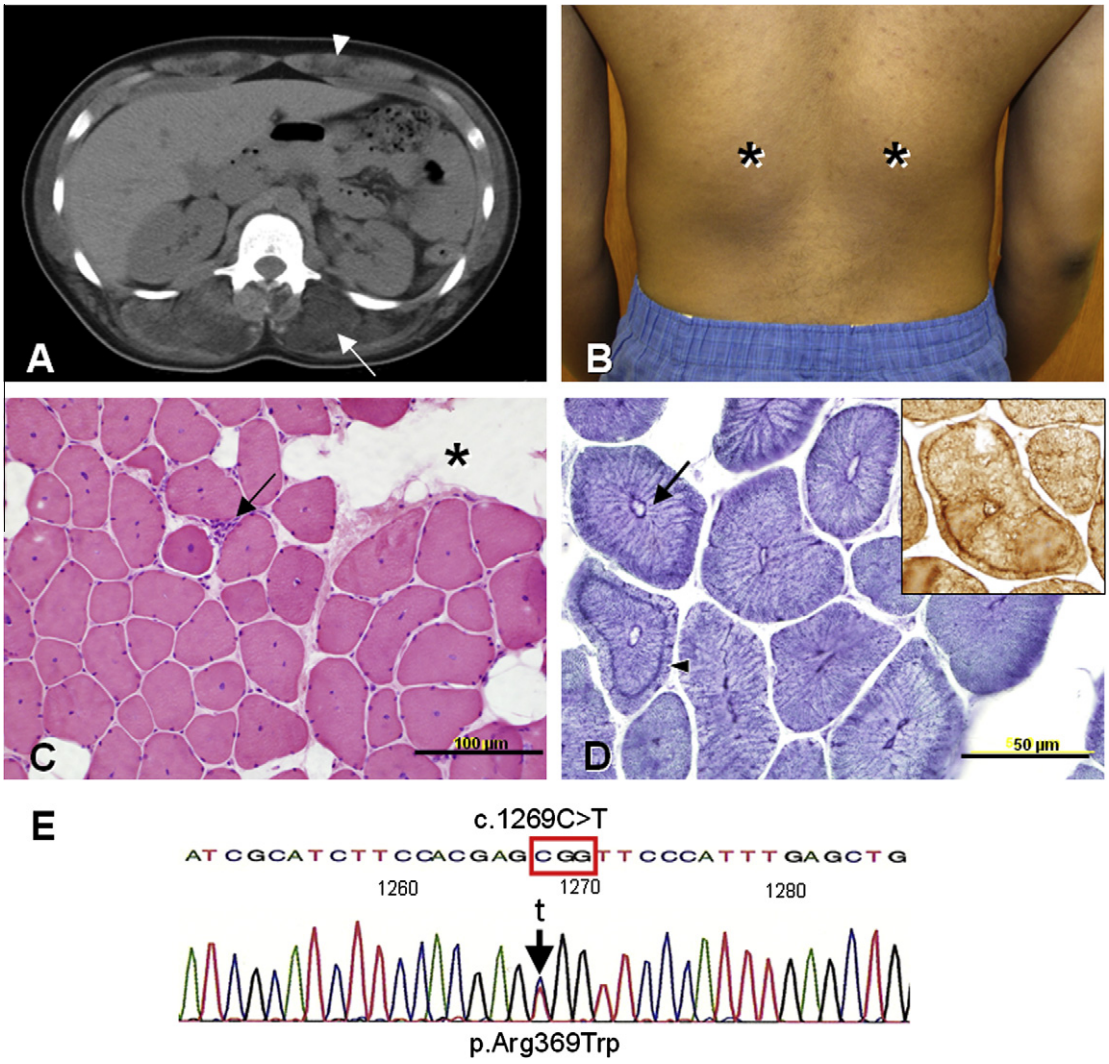

Fig. 1. (A) Abdominal CT scan reveals fatty infiltration and enlargement of paraspinal (arrow) and anterior abdominal muscles (arrowhead). (B) The patient with bilateral, paraspinal muscle (asterisk) hypertrophy. (C) Hematoxylin and eosin section displays numerous myofibers harboring centrally-place nuclei. Arrow points to a single necrotic fiber replaced by macrophages. There is a moderate to marked increase in perimysial fatty (asterisk) and a mild increase in endomysial fibrous connective tissue. (D) In NADH dehydrogenase-reacted section, some fibers show radial arrangement of the myofibrils and harbor central nuclei (arrow). Scattered myofibers with centrally-located nuclei displays peripheral accentuation of enzyme reactivity in a necklace-like pattern (arrowhead). The necklaces were positive for Sarcoplasmic/Endoplasmic reticulum calcium ATPase 2 (SERCA2) (inlet). (E) Chromatogram shows a heterozygous c.1269C > T substitution in *DNM2* exon 8 causing p.Arg369Trp. Bar: 100 μm in (C) and 50 μm in (D).