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Case report

Widening the spectrum of filamin-C myopathy: Predominantly proximal myopathy due to the p.A193T mutation in the actin-binding domain of *FLNC*

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Abstract

We report three patients with a predominantly proximal myopathy due to p.A193T mutation in the actin-binding domain of *FLNC*, which has so far only been associated with a distal myopathy. They presented with a late onset myopathy characterized by predominant limb-girdle and proximal weakness. We describe the clinical, electrophysiological, pathological, muscle imaging and genetic features. One of our patients did not have typical histological features for a myofibrillar myopathy in muscle biopsy. This observation is important for the recognition of the full clinical spectrum of filamin-C-related myopathies. Muscle imaging has an important role in distinguishing the different filamin-C myopathy types.

Keywords: Myopathy; Filamin-C; FLNC mutation

1. Introduction

Filamin-C-related myopathies are autosomal dominant inherited myopathies caused by mutations in *FLNC*, the gene encoding filamin-C. Three distinct types of myopathies have been described [1–4]. First, pathogenic mutations in the rod domain of *FLNC* generally cause a myofibrillar myopathy (MFM), histologically defined and characterized by focal disintegration of myofibrils and by formation of large sarcoplasmic protein aggregates [5]. MFM-filamin-C myopathy is usually associated with slowly progressive weakness predominantly affecting proximal muscles and starting in the fourth-to-sixth decade of life [1,6,7]. The two other filamin-C myopathy types have been described as distal myopathies with histological features not fulfilling the criteria required for diagnosis of MFM. One is caused by a frameshift mutation in *FLNC* that leads to a haploinsufficiency [2] and the other by missense mutations in the actin-binding domain of filamin-C resulting in increased actin binding affinity [3].

We here describe three patients from two non-related families with a p.A193T mutation in the actin-binding domain of *FLNC*, all presenting with a predominantly proximal myopathy but with a more variable phenotype than the MFM subtype. This report thus adds to the clinical spectrum of filamin-C-related myopathies and can aid in clinical recognition of this rare disorder.

2. Case report

2.1. Patient 1

A 53-year-old woman presented with mildly elevated serum creatine kinase levels (301 U/l) and gradually progressive limb girdle weakness since her forties. Initially, this was considered to be secondary to hypothyroidism and statin use. However, supplementation of thyroid hormone and cessation of statin therapy had not reduced her symptoms. Her walking distance

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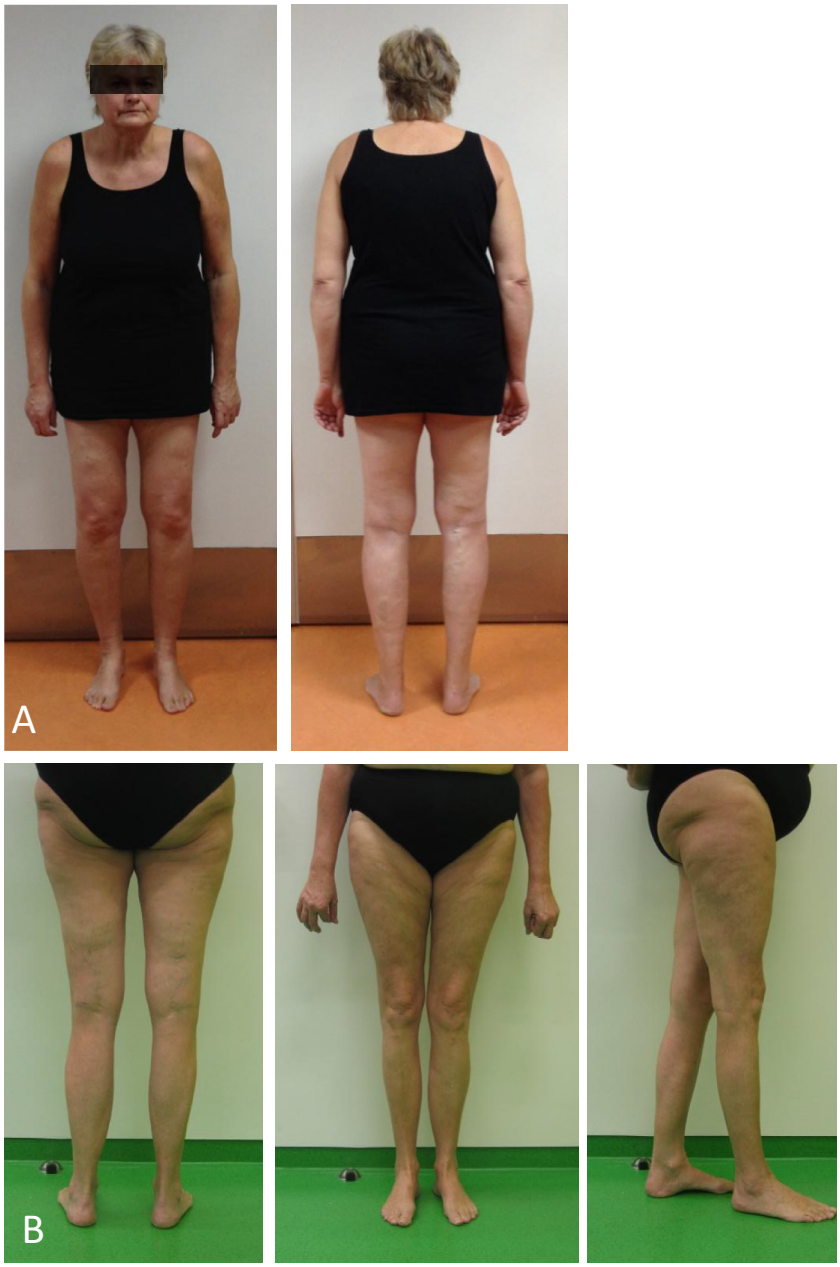

Fig. 1. Proximal and distal muscle atrophy in patient 1 (A) and patient 3 (B).

was limited to 500 metres, she could not run anymore and had difficulties climbing stairs. She experienced a feeling of weakness at the knees, without experiencing falls. She had kyphoscoliosis since childhood and had never been good at sports. Her medical history included a short episode of cardiac arrhythmia which was successfully treated with ACE inhibitors. Her mother, grandmother and great aunt also had slowly progressive muscle weakness, but without a specific diagnosis.

Physical examination revealed muscle weakness in truncal muscles, infraspinatus and supraspinatus muscles (MRC 4/5), neck flexion [4], hip flexion [4] and hip extension [2]. Distal strength in her arms was normal. Gowers' sign was present. The gait was waddling and walking on toes and heels was not possible. Atrophy was present in distal legs and quadriceps muscles bilaterally (Fig. 1A). Deep tendon reflexes (DTR) were absent. Vibration, pain and temperature sense were reduced in both legs distally.

Electromyography (EMG; at age 48 years) of the anterior tibial, rectus femoris, biceps brachii, and deltoid muscles showed no myopathic changes (no small or polyphasic motor unit action potentials (MUAP)). Muscle biopsy (at age 48 years) from the lateral vastus muscle showed minor abnormalities: few hypertrophic and some atrophic fibres, and focal changes that could have been suggestive for fibre type grouping (Fig. 2A).

Oxidative staining showed some inhomogeneous pattern, occasionally with some core-like appearance (Fig. 2B), but electron microscopy (EM) did not exhibit a significant core