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Thomsen disease with ptosis and abnormal MR findings

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Abstract

Myotonia congenita is a non-dystrophic skeletal muscle disorder characterized by muscle stiffness and an inability of the muscle to relax after voluntary contraction caused by a mutation in the gene encoding skeletal muscle chloride channel-1 (*CLCN1*). We encountered a case of Thomsen disease with ptosis. A short tau inversion recovery MR imaging demonstrated high-intensity lesions in the levator palpebrae superioris muscles. Molecular genetic testing revealed a heterozygosity for the c.1439C>A (p.P480H) mutation in the *CLCN1* gene. The expression level of ClC-1 was significantly reduced on the sarcolemma of the biceps brachii muscle from the patient, compared with that from healthy volunteer. Functional analysis of the p.P480H mutation is required for further elucidating the pathogenesis of Thomsen disease.

Keywords: Autosomal dominant; Immunohistochemistry; MRI; Myotonia congenita; Skeletal muscle chloride channel-1 (*CLCN1*); Thomsen disease

1. Introduction

Myotonia congenita is a non-dystrophic skeletal muscle disorder characterized by muscle stiffness and an inability of muscle relaxation after voluntary contraction. Both, the autosomal dominant (Thomsen disease) and the autosomal recessive (Becker disease), types of this disorder are caused by a mutation in the gene encoding skeletal muscle chloride channel-1 (*CLCN1*). Thomsen disease is less common than Becker disease with the prevalence estimated to be approximately 1 in 400,000 [1]. Thomsen disease often has a wide range of presentations because almost all striated muscles can be involved. Most common clinical features are percussion myotonia, handgrip myotonia, warm-up phenomenon, generalized hypertrophy, and generalized muscle stiffness. Less common features include lid lag, lid myotonia, tongue myotonia, and muscle pain. Herein, we present a case of Thomsen disease that showed ptosis and abnormal MR findings in the levator palpebrae superioris muscles, without lid lag or lid myotonia.

2. Patients and methods

2.1. Case report

Herein, we present a case of a 21-year-old Japanese man born to non-consanguineous parents. His family history was positive for neuromuscular disorders; his mother, maternal grandfather, and maternal great-grandfather presented with generalized muscle stiffness (Fig. 1A). Maternal grandfather presented with ptosis, but the mother did not have ptosis and the ptosis in the great grandfather was not confirmed. The birth history was unremarkable. His family noticed a clumsiness in his upper and lower limbs in early childhood. At 10 years of age, he complained of difficulty in running with leg stiffness at the beginning of the motion; however, his daily activities were normal. He also belonged to a baseball team in his high-school. At 18 years, he developed stiffness and difficulty in ambulation and climbing stairs at the beginning of motion. After joining college, he complained of difficulty in opening the mouth at the beginning of food consumption; however, speech and swallowing were normal. On admission, at 22 years, he showed a generalized Hercules-like hypertrophy of the muscles. Neurological examination revealed ptosis enhanced by contralateral lid elevation (Fig. 1B) and tongue myotonia, although the patient denied lid myotonia, diplopia, dysarthria, and dysphagia. He had full strength throughout with grip and percussion myotonia. The myotonia decreased with repetitive

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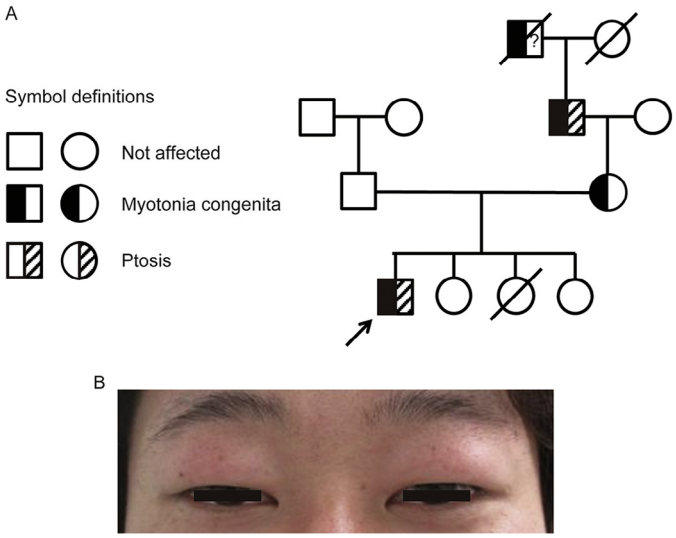

Fig. 1. Family pedigree of the family members. (A) Family members with myotonia or ptosis were indicated according to the symbol definitions. (B) A photograph of the proband's ptosis.

exercise (warm-up phenomenon). Reflex, sensation, and cerebellar testing were unremarkable. Laboratory examinations revealed no abnormalities including hemogram and serum levels of creatine kinase, glucose, and thyroid hormones. Holter electrocardiography showed no cardiac conduction impairment. Needle electromyography (EMG) detected spontaneous myotonic discharges with mild myogenic changes. High-frequency (50 Hz) repetitive nerve stimulation revealed approximately 25% reduction of compound muscle action potentials, whereas the short exercise test and cooling test showed no abnormalities. Skeletal muscle MRI showed no remarkable findings. Interestingly, short tau inversion recovery (STIR) imaging demonstrated high-intensity lesions in the levator palpebrae superioris muscles (Fig. 2). Molecular genetic testing revealed heterozygosity for the c.1439C>A (p.P480H) mutation in the *CLCN1* gene. Genetic testing showed no CTG repeat expansion in the *dystrophia myotonica-protein kinase (DMPK)* gene. Thereafter, sodium channel blocker mexiletine (300 mg/day) was administered because his symptoms including myotonia interfered with his daily life. However, the medication did not improve general symptoms as well as ptosis.

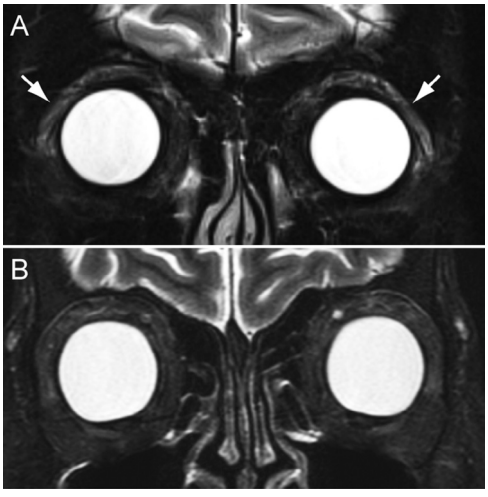

Fig. 2. Short tau inversion recovery (STIR) images of the patient (A) and healthy control (B). STIR images demonstrate high-intensity lesions in the levator palpebrae superioris muscles (arrows) in our case compared to that in healthy control.

2.2. Histological analyses

A muscle biopsy from the right biceps brachii muscle showed discrete myopathic changes including moderate variation in fiber size and internally located nuclei, without endomysial or perimysial cellular inflammatory infiltrates (Fig. 3A, B). ATPase stain showed no fiber type predominance. Immunohistochemistry using anti-CIC-1 antibody (1:200, ab189857, Abcam plc, Cambridge, UK) demonstrated less immunoreactivity for CIC-1 on the sarcolemma of the biopsied muscle (Fig. 3C, E), compared to that of the muscle samples from healthy volunteers (Fig. 3D, F). Quantification of immunofluorescence for ClC-1 revealed a smaller area and a less integrated density for ClC-1 in the biopsied sample than in control samples (Fig. 3G, H).

3. Discussion

We present a case of a patient who developed generalized muscular hypertrophy, and percussion and handgrip myotonia inherited as an autosomal dominant trait. Myotonia was most evident after rest and decreased with exercise repetition; however, it did not increase with cold. EMG revealed myotonic discharges, whereas muscle biopsy showed no dystrophic change. Genetic analysis of the *CLCN1* gene identified a known mutation, leading to the diagnosis of Thomsen disease.

The *CLCN1* gene, located on chromosome 7q35 [2], encodes the major skeletal muscle voltage-gated chloride channel ClC-1. The functional ClC-1 channel is a homodimer with a double-barreled architecture [3,4]. ClC-1 functionally maintains the membrane potential. The mutations have been thought to lead to decreased chloride conductance in the muscle membrane resulting in muscle hyper-excitability. Although more than 200 mutations have been identified in patients with myotonia congenita inherited in a dominant or recessive manner; so far [3], there is no hot spot and the mutations are scattered over the entire sequence of the gene [1]. A significant number of mutations associated with dominant myotonia congenita were identified in exon 8. The mechanism by which dominant mutations cause myotonic phenotype is expected to exert a dominant-negative effect on the associated wild-type subunit by disrupting the slow gate of the channel thereby altering or impairing the dimerization process [5].

Lid lag, lid myotonia, and to a lesser extent, impaired saccadic eye movement have been reported as ocular symptoms because almost all striated muscles including extraocular, facial, and lingual muscles can be affected [6]. However, myotonia is more evident in the limbs and the frequency of ocular symptoms is much less in chloride channel-related myotonia congenita compared to that with sodium channel-related disorders [6,7]. Our case showed bilateral ptosis without lid myotonia, lid lag,