Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.3417-23
Intern Med 63: 3371-3375, 2024
http://internmed.jp

【 CASE REPORT 】

X-linked Myotubular Myopathy Manifesting Carrier with Central and Peripheral Nervous System Involvement

Yosuke Takeuchi[1], Teruaki Masuda[1], Noriyuki Kimura[1], Kaori Sumi[1], Mika Jikumaru[1], Nobuyuki Eura[2], Ichizo Nishino[2] and Etsuro Matsubara[1]

Abstract:

X-linked myotubular myopathy (XLMTM) is a rare genetic disorder caused by X-linked mutations in the *MTM1* gene. Although heterozygous females are typically asymptomatic, affected cases have recently been reported. We herein report a case of XLMTM manifesting carrier of the pathogenic c.206dupG mutation in *MTM1* with uncommon extramuscular symptoms. She developed gaze nystagmus and cognitive impairment in addition to muscle weakness. Electrophysiological studies and brain magnetic resonance imaging indicated the involvement of the central and peripheral nervous systems. XLMTM manifesting carriers may have a wider spectrum of clinical phenotypes than currently assumed. Appropriate follow-up of extramuscular and conventional muscular manifestations is important in such cases.

Key words: X-linked myotubular myopathy, manifesting carrier, *MTM1* gene, extramuscular symptoms, nervous system involvement

(Intern Med 63: 3371-3375, 2024)
(DOI: 10.2169/internalmedicine.3417-23)

Introduction

A myotubularin 1 (*MTM1*) gene mutation is one of the causes of centronuclear myopathy, which is characterized by central nuclei fibers in skeletal muscles, and exhibits X-linked myotubular myopathy (XLMTM), an X-linked hereditary form in male patients (1). XLMTM presents with the most severe clinical symptoms, including ophthalmoplegia, dysphagia, weakness of the face and proximal extremities, and respiratory failure at birth, which contribute to a poor prognosis (2). As XLMTM is considered to be a recessive X-linked disease, heterozygous females are typically asymptomatic. However, several female patients with muscle weakness of the face and extremities and respiratory failure have been reported (3, 4) and they are called manifesting carriers. A recent study showed that the prevalence of manifesting carriers was higher than previously assumed (5). Therefore, a more appropriate assessment and management of muscular symptoms are needed to identify manifesting carriers of XLMTM. The presence of extramuscular symptoms has also been reported in a few cases, but the clinical phenotype remains unknown (5, 6).

We herein report a case of XLMTM manifesting carrier with a novel frameshift mutation in the *MTM1* gene that presented with central and peripheral nervous system involvement.

Case Report

A 55-year-old woman presented to our hospital with progressive weakness of the face and extremities. Although she had no postnatal development problems, she was a slow runner in kindergarten. At 25 years of age, the patient developed left-sided facial weakness. Weakness of the right limbs started at 48 years of age, and she tended to fall easily from 52 years of age. Her gait disturbance progressed, thus necessitating the use of a walker at 57 years of age. She also developed some mild cognitive decline at 60 years of age. To the best of our knowledge, none of her family members experienced any similar symptoms (Fig. 1).

A neurological examination revealed bilateral ptosis, hori-

[1]Department of Neurology, Faculty of Medicine, Oita University, Japan and [2]Department of Neuromuscular Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Japan
Received: December 27, 2023; Accepted: March 1, 2024; Advance Publication by J-STAGE: April 16, 2024
Correspondence to Dr. Teruaki Masuda, terumasu@oita-u.ac.jp

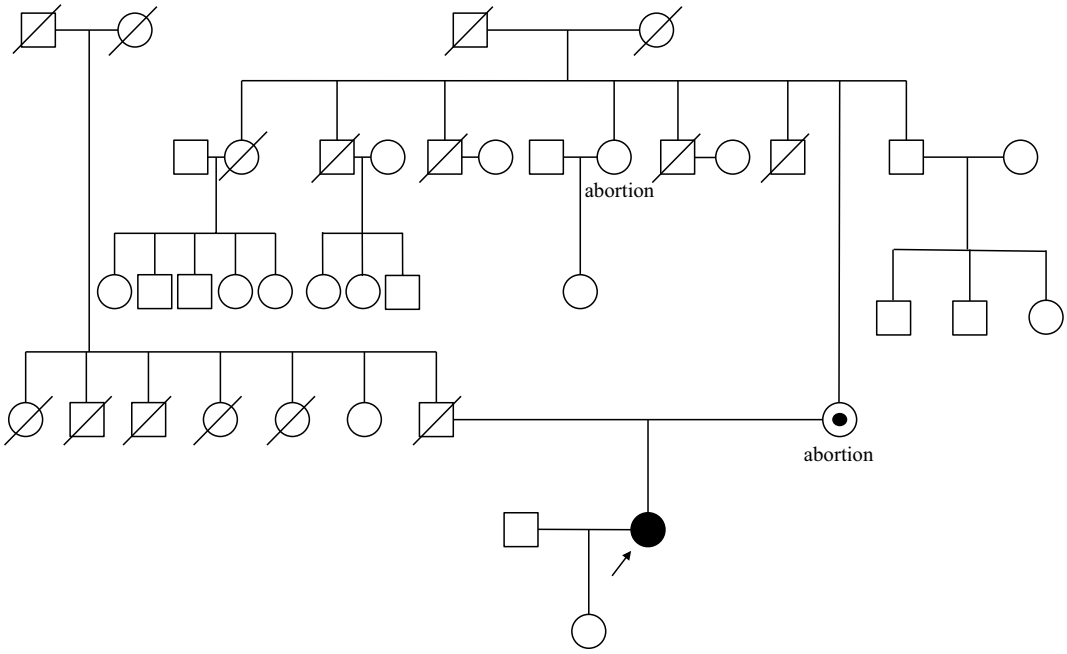

Figure 1. **The patient's family tree. None of the patient's family member demonstrated any similar symptoms.**

Table. **Electrophysiological Study Findings.**

Nerve conduction study (left side)						
	DL (ms)	CMAP (mV)	MCV (m/s)	F latency (ms)	SNAP (μV)	SCV (m/s)
Median nerve	4.8	5.6	53.8	25.6	26.1	46.4
(Normal range)	<4.6	>3.0	>49.5	<28.2	>7.0	>47.1
Ulnar nerve	3.4	5.1	41.8	25.2	35.6	51.7
(Normal range)	<3.8	>5.8	>49.9	<29.7	>6.9	>46.8
Tibial nerve	4.0	12.2	39.1	51.1		
(Normal range)	<5.7	>4.3	>41.6	<51.7		
Peroneal nerve	3.3	5.3	36.0	NE		
(Normal range)	<6.8	>4.0	>42.7	<51.7		
Sural nerve					7.3	46.7
(Normal range)					>7.4	>40.7

Auditory brainstem response (80 dB nHL)						
	I wave latency (ms)	III wave latency (ms)	V wave latency (ms)	I-III interpeak latency (ms)	III-V interpeak latency (ms)	I-V interpeak latency (ms)
Right side	1.68	4.67	6.54	2.99	1.87	4.86
Left side	1.52	4.74	6.29	3.22	1.55	4.77
(Normal range)	<1.7	<3.9	<6.0	<2.3	<2.0	<4.3

DL: distal latency, CMAP: compound muscle action potential, MCV: motor conduction velocity, SNAP: sensory nerve action potential, SCV: sensory conduction velocity, NE: not evaluated

zontal gaze nystagmus, weakness in the left orbicularis oculi and orbicularis oris muscles, neck flexors, and extremity muscles, a reduced sense of vibration in the bilateral lower extremities, hyporeflexia in the upper extremities, and gait disturbance. There were no signs of vertical nystagmus, dysarthria, or intention tremors. Limb and truncal ataxia were not clearly evident because of moderate weakness in the limb muscles. The Mini-Mental State Examination, Revised Hasegawa Dementia Scale, and Japanese version of the Montreal Cognitive Assessment scores were 26/30, 27/30, and 20/30, respectively. She demonstrated no symptoms of heart, liver, bladder, or gastrointestinal dysfunctions. The serum levels of hemoglobin A1c, thiamine, cobalamin, folic acid, angiotensin-converting enzyme, and soluble

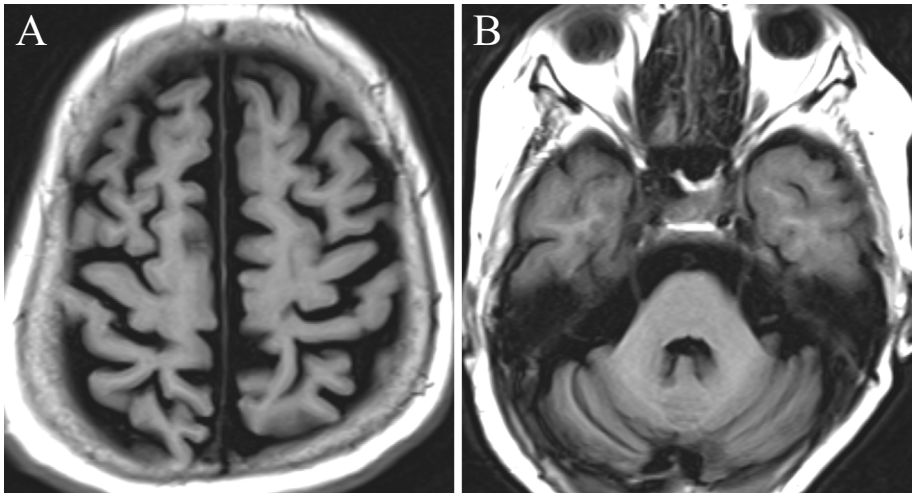

Figure 2. **Brain magnetic resonance imaging (MRI). Brain MRI showing cerebral and cerebellar atrophy on axial T1-weighted images (A and B, respectively).**

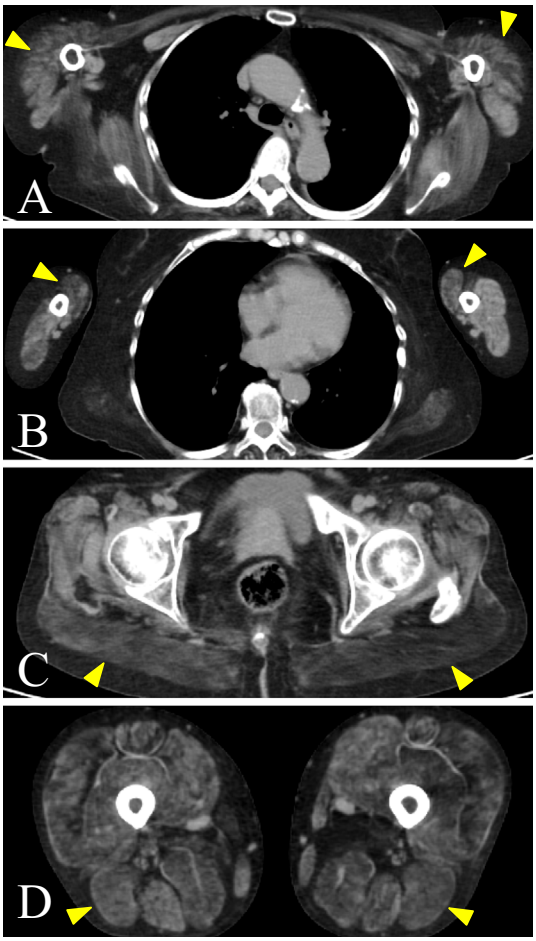

Figure 3. **Skeletal muscle computed tomography (CT). Skeletal muscle CT demonstrates asymmetric atrophy in the bilateral deltoid muscles (A, arrowheads), biceps brachii muscles (B, arrowheads), gluteus maximus muscles (C, arrowheads), and hamstring muscles (D, arrowheads).**

interleukin-2 receptor were all within normal ranges. The levels of anti-nuclear, anti-SS-A, anti-SS-B, anti-neutrophil cytoplasmic, anti-aquaporin 4, anti-myelin oligodendrocyte glycoprotein, anti- neurofascin 155, anti-paraneoplastic antibodies, and monoclonal proteins were all normal. A routine cerebrospinal fluid analysis indicated a normal cell count, protein levels, immunoglobulin G index, and myelin basic protein, with no oligoclonal bands. Spirometry revealed a mixed ventilatory impairment (%VC, 67.4%; %FVC, 68.8%; FEV_1% 50.3%). A nerve conduction study (NCS) showed mild demyelination of the peripheral nerves (Table). Needle electromyography identified myogenic changes in the biceps brachii muscle. Regarding the auditory brainstem response (ABR) at 80 dB nHL, the I-III interpeak latency was extended, thus indicating a brainstem dysfunction (Table). Electronystagmography demonstrated saccadic pursuit in the eye-tracking test, poor resolution of optokinetic nystagmus, and normal findings in the caloric test, suggesting an impairment in the brainstem and cerebellum. Brain magnetic resonance imaging (MRI) revealed cerebral and cerebellar atrophy (Fig. 2). Brain perfusion single photon emission computed tomography (SPECT) revealed a reduced blood flow in the bilateral frontal and parietal lobes. Cognitive impairment, gaze nystagmus, ABR, NCS, brain MRI, and perfusion SPECT indicated central and peripheral nervous system dysfunctions. Skeletal muscle computed tomography revealed severe asymmetric atrophy in the bilateral deltoid, biceps brachii, gluteus maximus, and hamstring muscles (Fig. 3). A biopsy of the left biceps brachii muscle demonstrated myopathic changes with centrally nucleated fibers, a peripheral halo, necklace fibers, and type 1 fiber predominance, in addition to fiber size variation (Fig. 4). A sural nerve biopsy was not performed because of the patient's refusal.

After obtaining informed consent, we analyzed *MTM1* cDNA from peripheral leukocytes using a sequence analysis, which revealed a novel mutation in *MTM1*, c.206dupG (p.L 70Sfs*15). Notably, the patient's mother also possessed the same mutated allele. Based on the clinical findings, muscle biopsy, and genetic analysis, an XLMTM manifesting carrier

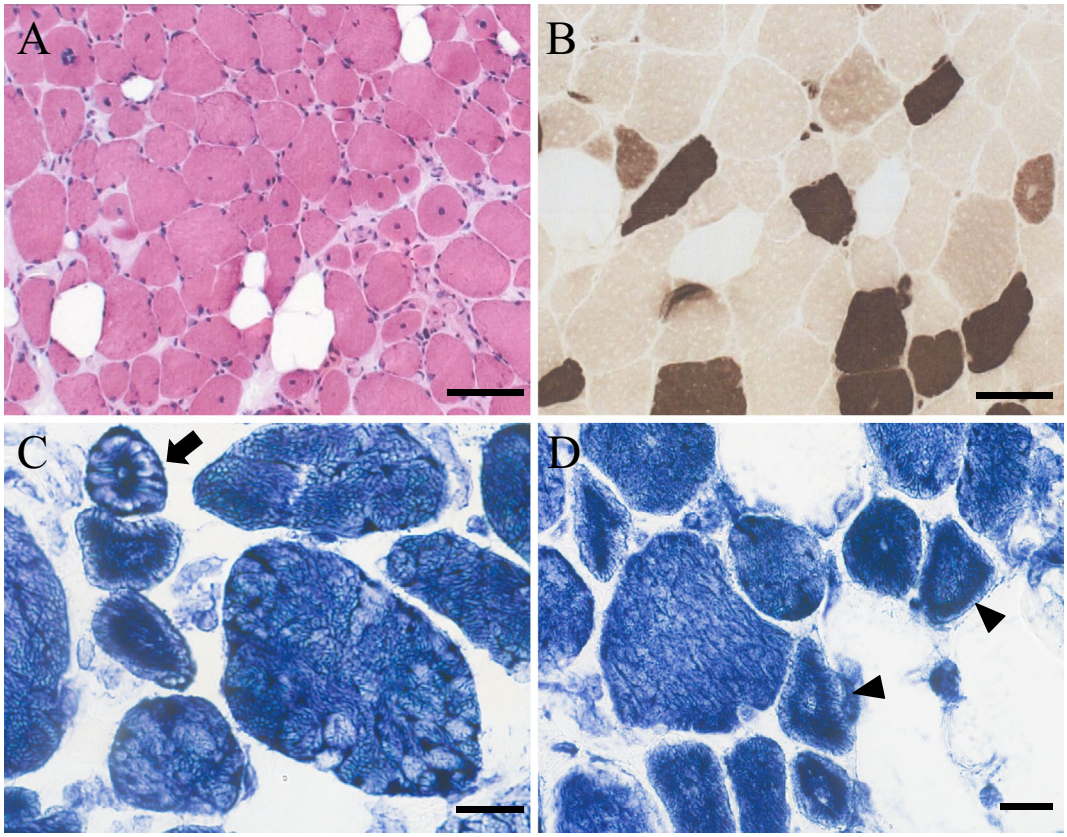

Figure 4. **Pathological findings of a muscle biopsy. A muscle biopsy shows fiber size variation and many fibers with central nuclei in Hematoxylin and Eosin staining (A, bar=50 μm), type 1 fiber predominance in myosin ATPase staining with preincubation at pH 10.4 (B, bar=50 μm), and peripheral halo (C, arrow, bar=20 μm) and necklace fibers on nicotinamide adenine dinucleotide- tetrazolium reductase staining (D, arrowheads, bar=20 μm).**

was thus diagnosed.

Discussion

We herein present the case of a patient who developed muscle weakness and various features of the nervous system, such as nystagmus, cognitive impairment, and peripheral neuropathy. A muscle biopsy revealed many central nuclear fibers, peripheral halos, and necklace fibers. A genetic analysis of *MTM1* identified a novel frameshift mutation, which led to the diagnosis of XLMTM manifesting carrier. Moreover, neuropsychological testing and brain MRI indicated a dysfunction of the central and peripheral nervous systems.

The asymmetric weakness of the face and extremities in the present case is consistent with previously reported cases of XLMTM manifesting carriers (3, 7, 8). Interestingly, our patient presented with uncommon symptoms, such as cognitive impairment and horizontal gaze nystagmus, as well as common muscle symptoms. Although the association between *MTM1* gene mutations and nervous system involvement is unclear, there are previously documented cases of patients with XLMTM cognitive impairment (9) and peripheral demyelinating neuropathy (10). Myotubularin is a 3-phosphatase specific for phosphatidylinositol 3-phosphate (PI(3)P) and PI(3,5)P2 and it is widely expressed throughout the body, including the brain (11). The misregulation of PI (3,5)P2 causes neurodegeneration in mice (12, 13). In our case, the *MTM1* frameshift mutation possibly disrupted the synthesis of proteins in the myotubularin family and thus impaired the central and peripheral nervous systems.

However, this is the first reported case of XLMTM with a dysfunction of the brainstem and cerebellum, and it is unclear whether the observed brainstem and cerebellar impairments are related to *MTM1* gene mutations. Furthermore, whole-exome sequencing was not performed because of a lack of consent from the patient, and we could not definitively exclude the involvement of other genetic variants regarding the neurological symptoms. Additional cases are needed to uncover the association between *MTM1* mutations and nervous system involvement.

Why do heterozygous female carriers develop symptoms of X- linked recessive inheritance? One possible explanation is skewed X-chromosome inactivation, similar to other X-linked hereditary diseases such as Duchenne muscular dystrophy and Fabry disease (3, 14, 15). This skewed X-chromosome inactivation may also influence the symptom diversity. Another possibility is that the killer cell immunoglobulin-like receptor cluster of genes is present in non-manifesting carriers, but absent in manifesting carriers,

which may indicate that killer cell immunoglobulin-like receptor variants act as protective factors, thus regulating the phenotype of non-manifesting carriers (16).

The relationship between genotype and disease severity in XLMTM manifesting carriers remains unknown. In male patients with XLMTM, nonsense and frameshift mutations in *MTM1* mostly cause severe symptoms, whereas missense mutations result in milder symptoms (1, 17). Our patient presented with a frameshift mutation in *MTM1* that induced a nonsense codon in exon 5, potentially contributing to the relatively severe phenotype observed. XLMTM manifesting carriers may also develop various abnormalities, such as cardiac valve insufficiency, asthma, and spastic paraplegia (5, 6). Further studies are needed to investigate the association between the genotype and phenotype, including disease severity, in XLMTM manifesting carriers.

In conclusion, we described a case of XLMTM manifesting carrier with various neurological features, including nystagmus, cognitive impairment, and peripheral neuropathy, in addition to conventional muscular symptoms. Although the origin of the neurological symptoms remains unclear in *MTM1* mutations, XLMTM manifesting carriers may have a broader spectrum of clinical phenotypes than currently acknowledged. It is difficult to properly diagnose this disease based on the clinical features alone, and it is important to detect the presence of centronuclear myopathy using muscle biopsies along with genetic testing. Furthermore, over time, this disease can present with a variety of symptoms involving the central and peripheral nervous systems, and appropriate follow-up should be performed while keeping these symptoms in mind in order to make a timely diagnosis and improve the quality of life of such XLMTM manifesting carriers.

The authors state that they have no Conflict of Interest (COI).

Financial Support

This study was partly supported by an Intramural Research Grant 5-6) for Neurological and Psychiatric Disorders of the National Center of Neurology and Psychiatry.

Acknowledgement

We would like to thank all the members of the Department of Neurology, Oita University Hospital, for helping with the collection of clinical data.

Yosuke Takeuchi and Teruaki Masuda contributed equally to this work.

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