Brain & Development 41 (2019) 470–473

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Case Report

Phenotype of a limb-girdle congenital myasthenic syndrome patient carrying a *GFPT1* mutation

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Received 29 March 2018; received in revised form 11 September 2018; accepted 17 December 2018

Abstract

We report a 38-year-old woman who presented with mild proximal dominant muscle weakness and fatigability that fluctuated during menstruation and treatment with ephedrine-containing medication. The patient had been diagnosed with "congenital myopathy with tubular aggregates" by muscle biopsy at age 19. Her revised diagnosis was congenital myasthenic syndrome (CMS) caused by a mutation in *GFPT1* (2p13.3 [MIM 610542], c.722_723insG homozygote, CMS-GFPT1) based on a screening gene analysis. Muscle CT revealed diffuse atrophy of proximal and axial muscles focused on the vastus lateralis, hamstrings, medial gastrocnemius and soleus muscles. Oral administration of pyridostigmine bromide clearly ameliorated weakness and fatigability. This is the first reported case of CMS-GFPT1 in Japan. Since CMS symptoms are reactive to treatment, it is important for clinicians to make an accurate diagnosis at an early stage to improve patient QOL. Tubular aggregates in muscle biopsy and day-to-day fluctuations are important features of the disorder. Quantitative muscle strength measurement was effective for evaluating treatment efficacy.

1. Introduction

Glutamine-fructose-6-phosphate transaminase 1 (GFPT1) is the initial and rate-limiting enzyme in the biosynthesis of N-acetylglucosamine, an essential substrate for O- and N-glycosylation [1]. There are two splice variants of GFPT1, yielding a ubiquitous GFPT1 isoform and a long muscle-specific isoform (GFPT1-L) expressed predominantly in skeletal muscle and the heart. A mutation in *GFPT1* (GenBank Accession number OMIM 138292) causes a subtype of limb-girdle congenital myasthenic syndrome (CMS: OMIM 610542) that presents with prominent shoulder and pelvic girdle weakness and fatigue with minimal ocular and facial involvement [2,3]. Tubular aggregates found in muscle biopsies are key diagnostic features [4]. CMS patients carrying the *GFPT1* mutation (CMS-GFPT1 patients) respond well to AChE inhibitors, 3,4-diaminopyridine, ephedrine and/or beta stimulants [2–8].

Here we present the first reported case of CMS due to *GFPT1* mutation in Japan. The patient's symptoms showed obvious fluctuations during menstruation and with ephedrine administration. Detailed clinical diagnostic features, muscle imaging and the method of therapeutic evaluation are reported.

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https://doi.org/10.1016/j.braindev.2018.12.002

2. Case report

The patient was a 38-year-old Japanese woman. She had no family history relevant to muscle weakness, and was not from a consanguineous marriage. Her developmental milestones were normal. She achieved head control at age 3 months and took her first steps at age 18 months, but she walked slower than other children and had difficulty running. She was diagnosed with congenital myopathy by muscle biopsy at age 8. At age 10, she was no longer able to run and felt fatigue when walking. At age 13, she became unable to raise her arms above her shoulders and her grip strength weakened. She required handrails when using stairs. Onset of menstruation was at age 15. Since age 18, she has experienced fatigue, headache and difficulty moving during menstruation. She underwent a neurologic examination that revealed a waddling gait, proximal weakness, mild facial weakness without ptosis and intact extraocular movements. A second muscle biopsy of the right rectus femoris showed mild myopathic changes with some muscle fibers containing tubular aggregates (Fig. 1), resulting in a diagnosis of congenital myopathy with tubular aggregates. Thereafter, her symptoms remained immutable, but became exacerbated during menstruation. When she took ephedrine-containing medication for flu, her symptoms improved to the extent she could climb stairs with little need for handrails. She was more easily fatigued compared to her friends. She never experienced dysphagia even when she had the flu or during menstruation. When she was age 37, genetic analysis of genomic DNA by whole exome sequencing at the National Center of Neurology and Psychiatry revealed a heterozygous mutation in *AGRN*, heterozygous mutation in *CNRB1* and homozygous mutation in *GFPT1* (c.722_723insG), i.e., known causative genes for CMS. While the two heterozygous mutations can been found in a public database of the normal population (allele frequency in ExAC_EAS: 0.0008 for *AGRN* and 0.0092 for *CNRB1*), the *GFPT1* mutation (c.722_723insG) is a novel mutation that has not been reported previously. The c.722_723insG mutation in *GFPT1* may cause p. G241fs, which leads to loss of the entire isomerase domain. Accordingly, she was diagnosed with CMS-GFPT1.

On neurological examination, she had no ptosis, ophthalmoplegia, facial weakness or arched palate. Decreased muscle tone and diffuse mild muscle atrophy were observed in all proximal extremities. She could neither keep her head elevated in the supine position nor keep her upper limbs raised for more than 4 min. Manual muscle tests (MMT) performed to evaluate proximal dominant muscle weakness showed that axial, shoulder and girdle muscles were grade 2, and other muscles were grade 4. The examination also revealed axial muscle atrophy and winged scapulae. A repetitive hand gripping task showed a significant decrease in grip power from 13.4 kg to 9.3 kg (31% decrease) for the right hand. She had a waddling gait and Gower's sign. No other abnormalities were noted. Laboratory findings revealed normal levels of creatine kinase (CK, 121 IU/l). Anti-AChR antibodies and anti-MuSK antibodies were not detected. Arterial blood gas was normal. Pulmonary function test revealed mild respiratory dysfunction (VC 2.08 L; %VC 74.5%). No cardiac involvement was found. Needle electromyography showed chronic myogenic changes without spontaneous activity. A repetitive stimulation test performed on the right median nerve revealed 22.5% attenuated compound motor action potential with low frequency stimulation (3 Hz) (Fig. 2). Muscle CT revealed diffuse atrophy in upper extremities and truncal muscles, whereas lower extremities showed certain selectivity (Fig. 3). The vastus lateralis, biceps short head, semitendinosus and semimembranosus muscles showed significant atrophy and fatty replacement in the thigh. The medial gastrocnemius and soleus muscles were significantly affected in the lower leg.

Intravenous injection of edrophonium chloride improved the time required for going up and down stairs (12 steps) from 30.7 s to 26.2 s. The time required for

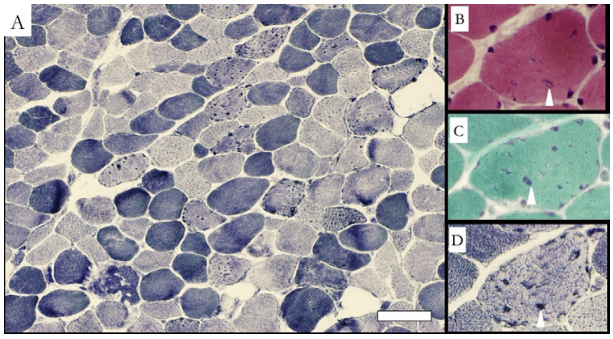

Fig. 1. Muscle biopsy specimens at age 18. NADH-Tr staining shows scattered fibers with tubular aggregates (A, D). Tubular aggregates are also found with HE (B) and modified Gomori trichrome staining (C) (white arrowheads).

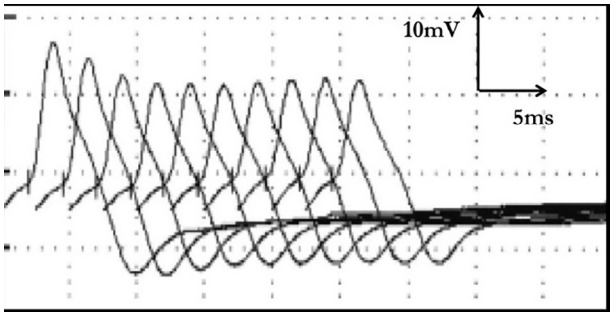

Fig. 2. Repetitive stimulation test performed in the right median nerve revealed 22.5% attenuated compound motor action potential with low frequency stimulation (3 Hz).

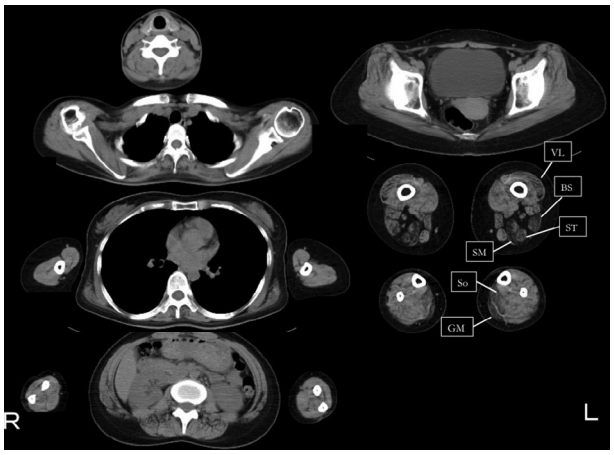

Fig. 3. Muscle CT at age 38. Diffuse atrophy is evident in upper extremities and truncal muscles, whereas lower extremities showed selectivity. Significant atrophy and fatty replacement are observed in the vastus lateralis (VL), biceps short head (BS), semitendinosus (ST) and semimembranosus (SM) muscles. In the lower leg, the medial gastrocnemius (GM) and soleus (So) muscles were significantly affected.

squatting improved from 7.92 s to 6.36 s. No change was observed on repetitive stimulation tests after edrophonium chloride injection.

She responded well to pyridostigmine bromide (120 mg/day) and felt it easier to climb stairs than before. The time required for going up and down stairs decreased from 30.7 to 20.0 s (32.6% improvement), and the time required for squatting decreased from 7.92 to 4.56 s (41.8% improvement). MMT of knee extension improved from 4 to 5. The repetitive hand gripping task showed a reduction in the decrease in grip power (13.4 kg–9.3 kg, 31% decrease before treatment; 16.8 kg–14.9 kg, 9% decrease after treatment), and initial grip power also improved by 25%. The medication did not improve performance on the repetitive nerve stimulation test or the respiratory test. The patient felt the effects of medication begin about 1 h after administration for up to 6–7 h. By taking medication twice daily (after breakfast and lunch), the patient did not feel fatigue until night. The remaining fatigue resolved when the amount of medication was increased to 240 mg three times daily. To date, her symptoms and respiratory function have been stable for five years, with no side effects. Ephedrine and procaterol hydrochloride hydrate did not prove effective.

3. Discussion

This is the first reported case of CMS-GFPT1 in Japan. We provide detailed information regarding the clinical course of illness, muscle imaging and quantitative data showing improvement after pyridostigmine bromide treatment (120 mg/day). This first report of deterioration during menstruation in a patient with CMS-GFPT1 is consistent with previous reports of CMS patients carrying mutations in *Musk* [9] or *Dok7* [10]. She also noticed improvement after administration of flu medication that included ephedrine, which is known to have a therapeutic effect in CMS patients. These fluctuations are important clinical diagnostic features, together with limb-girdle weakness and early fatigability.

This is also the first report of muscle imaging in a CMS-GFPT1 patient. CT revealed diffuse muscle atrophy, but primarily in the vastus lateralis, hamstrings, medial gastrocnemius and soleus. Axial atrophy and quadriceps weakness are compatible with lordosis, waddling gait and Gower's sign.

To date, 58 CMS-GFPT1 cases with clinical details have been published [2–8]. Only a few patients had respiratory dysfunction [2,5]. Our patient did not exhibit respiratory symptoms or hypoxia, but patients with CMS-GFPT1 may suffer from mild respiratory dysfunction.

We clearly described the effects of therapeutic interventions in this patient. Descriptions of improvement after treatment are sometimes ambiguous and difficult to compare over time. Quantitative evaluation of improvement simplified the clinical evaluation of efficacy and follow-up.

In conclusion, CMS-GFPT1 is a possible diagnosis for patients with limb-girdle weakness and symptom fluctuation, especially during menstruation and when taking ephedrine-containing medication.

Acknowledgements

This work was partly supported by Research on Intractable Diseases of Health and Labor Sciences Research Grants, Comprehensive Research on Disability Health and Welfare Grants, Research and Development Grants for Comprehensive Research for Persons with Disabilities, and the Practical Research Project for Rare/Intractable Diseases from the Japan Agency for Medical Research and Development (AMED), Health and Labor Science Research Grants, and an Intramural Research Grant (**29-3, 29-4**) for Neurological and Psychiatric Disorders from the NCNP.

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