Parasympathetic Dominant Autonomic Dysfunction in Charcot-Marie-Tooth Disease Type 2J with the MPZ Thr124Met Mutation

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Abstract

We herein report the case of a 69-year-old woman with Charcot-Marie-Tooth Disease type 2J (CMT2J) who presented with Adie’s pupil, deafness, and urinary disturbance in addition to motor symptoms. On autonomic investigation, the coefficient of variation of the R-R intervals was decreased, and a urodynamic analysis showed a hypotonic bladder. A heart rate variability analysis revealed a decreased high frequency component and low frequency/high frequency ratio. Orthostatic hypotension was not present, and the sympathetic skin response and cardiac scintigraphy using ¹²³I-metaiodobenzylguanidine were normal. A gene analysis showed a known heterozygous mutation associated with CMT2J in myelin protein zero exon 3, resulting in the substitution of threonine to methionine at position 124. Our case suggests that mainly the parasympathetic autonomic function is disturbed in CMT2J.

Key words: Charcot-Marie-Tooth disease type 2J, MPZ Thr124Met mutation, autonomic dysfunction, Adie’s pupil, myelin protein zero


Introduction

Mutations of the gene encoding the major myelin protein of the peripheral nerves, myelin protein zero (MPZ), result in hereditary motor and sensory neuropathies, commonly referred to as Charcot-Marie-Tooth disease (CMT). To date, over 200 allelic mutations of the MPZ gene have been reported, and the phenotypes vary according to the mutation type. Based on nerve conduction studies, CMT is divided into three subtypes: demyelinating, axonal, and intermediate. All three subtypes are present in MPZ-associated CMT (1-3). In 1999, De Jonghe et al. and Chapon et al. reported families with an MPZ Thr124Met mutation that resulted in axonal-type CMT [CMT type 2J (CMT2J)]. Previous reports have described patients with CMT2J who presented with late-onset axonal neuropathies, marked sensory disturbances, deafness, and pupillary abnormalities (4-7). Although pupillary abnormality is a characteristic finding of CMT2J, there have so far been few detailed autonomic investigations in patients with CMT2J. We herein report an elderly Japanese patient with CMT2J, who presented with parasympathetic dominant autonomic dysfunction in addition to motor and sensory axonopathy.

Case Report

The patient was a 69-year-old woman who had been in good health until 18 years prior to this presentation when she noticed difficulty walking. At 61 years of age, she became aware of a subtle tingling sensation in her feet and experienced difficulty urinating. Gradually, she became unable to walk without assistance, at which time she visited our facility. She had no subjective symptoms involving vision dur-
A neurological examination of the patient revealed bilateral pupillary dilatation, markedly slow light and convergence reflexes, and bilateral hearing loss. Miosis was detected in response to 0.125% pilocarpine, which is indicative of Adie’s pupil. Moderate distal-dominant muscle atrophy of the lower legs and pes cavus was observed. The Medical Research Council scores were 0 for the extensor and flexor of the lower extremities, and severe hearing loss in the high frequencies. The sympathetic skin response (SSR) of the hand was normal. On cardiac scintigraphy using $^{123}$I-metaiodobenzylguanidine (MIBG), the MIBG heart-to-mediastinum ratio showed no decrease.

A nerve conduction study of the right median, ulnar, and tibial nerves revealed that the motor nerve conduction velocities of the three nerves were relatively well preserved (46.4, 59.0, and 38.6 m/s, respectively). On the other hand, the sensory nerve action potential (SNAP) amplitudes in the tibial nerve was markedly decreased (0.1 mV), and that in the peroneal nerve was not evoked. Similarly, sensory nerve conduction velocities of the right median, ulnar, and sural nerves were within the normal limits (49.4, 51.7, and 51.9 m/s, respectively). The sensory nerve action potential (SNAP) amplitudes in the three nerves were decreased (9.7, 10.1, and 6.0 μV, respectively). The symmetric and uniform decreases in the CMAP and SNAP amplitudes, in a length-dependent manner, suggested motor and sensory axonopathy. Needle electromyography of the first dorsal interosseous and tibialis anterior muscles showed active and chronic denervation. No nerve enlargement was observed on sonography of the peripheral nerves.

After obtaining written informed consent from the patient, DNA was extracted from her lymphocytes. Genetic testing revealed a known heterozygous mutation in MPZ exon 3, resulting in the substitution of threonine to methionine at position 124 (MPZ Thr124Met mutation). Consequently, we diagnosed the patient with CMT2J. Because informed consent was not obtained for a familial analysis, it was not performed.

**Discussion**

The MPZ Thr124Met mutation results in a unique CMT phenotype. In addition to mild motor and sensory axonopathy, autonomic dysfunction is pathognomonic of CMT. This case report describes autonomic dysfunction in a patient with CMT2J (MPZ Thr124Met mutation), which was parasympathetic dominant. In addition to mild motor and sensory axonopathy, our patient displayed Adie’s pupil, hypotonic bladder, decreased CV R-R, and a low HF component and LF/HF ratio in the HRV analysis. Adie’s pupil is caused by damage to the parasympathetic ganglion or the postganglionic fibers of the oculomotor nerve. Hypotonic bladder, decreased CV R-R, and a low HF component, according to a HRV analysis, also occur due to damage of the parasympathetic nervous system activity, while the LF/HF ratio reflects the nervous system activity (8). Both the HF component and LF/HF ratio were decreased to 22.9 ms² (<164.0 ms²: the mean in normal controls) and 2.14 (<4.14: the mean in normal controls), respectively. On cystometrography, no increase in the intravesical pressure was induced in response to the injection of 450 mL water, and the patient did not feel an imminent urge to urinate. Therefore, her dysuria was diagnosed as hypotonic bladder. The sympathetic skin response (SSR) of the hand was normal. On cardiac scintigraphy using $^{123}$I-metaiodobenzylguanidine (MIBG), the MIBG heart-to-mediastinum ratio showed no decrease.

Figure. Family pedigree. Squares: males, circles: females, diagonal line: deceased members, black-filled circle: the present case with the MPZ Thr124Met mutation, grey-filled circle: a family member with similar symptoms to those of the patient.
pathetic nervous system. On the other hand, a low LF/HF ratio reflects sympathetic nervous system dysfunction. However, she did not present with orthostatic hypotension, and the SSR and MIBG cardiac scintigraphy findings were normal. These findings indicate that autonomic dysfunction is parasympathetic dominant.

Four MPZ mutation foci that cause CMT2J have been identified (4-6, 9, 10), among which the Thr124Met mutation has been frequently reported. However, there have been few detailed autonomic investigations. Although Baloh et al. reported symptoms of dysautonomia (irritable bowel syndrome, occasional urinary incontinence, and erectile dysfunction) in addition to Adie’s pupil in the proband of a CMT2J family with the MPZ Thr124Met mutation, objective assessment of autonomic function was not performed (11). Nakamura et al. reported a male Japanese patient with the MPZ Thr124Met mutation who presented with erectile dysfunction, dysuria, photophobia, and chronic cough; an objective autonomic test revealed parasympathetic autonomic system dysfunction (12). Although our female patient did not present with chronic cough, parasympathetic dominance of the autonomic system dysfunction was confirmed by detailed autonomic tests, including a HRV analysis. The failure to examine her family members is a limitation of this study.

Manifestations of parasympathetic autonomic dysfunction, Adie’s pupil, and difficulty urinating were seen in our patient, which is consistent with previous studies. However, because she became aware of difficulty urinating in her 60s, dysuria was potentially due to aging in this case. Baloh et al. described a large CMT2J family with the MPZ Thr124Met mutation in whom chronic cough was one of the symptoms induced by parasympathetic autonomic dysfunction (11). They speculated that the selective loss of afferents originating in the lung, trachea, and larynx could lead to hypersensitivity of secondary neurons in the nucleus tractus solitarius, which results in chronic cough. On the other hand, hearing loss was not observed in the family. The patient in that report and those in certain previous studies did not exhibit coughing. Clinical manifestation varies slightly among patients with the MPZ Thr124Met mutation.

The MPZ protein accounts for approximately 50% of the total protein content of peripheral nerve myelin and plays major structural roles in the highly organized formation of myelin. CMT presenting with MPZ mutations is classified into three types: demyelinating (CMT1B), axonal (CMT2J, 2J), and intermediate (CMT DID). It remains unclear whether the gene mutation associated with myelin induces not only demyelination, but also axonal loss. Previous reports have speculated that subtle abnormalities in the myelin sheath may lead to aberrant Schwann cell-axon interactions that cause axonal degeneration over time (13, 14). The existence of autonomic nervous system dysfunction in CMT associated with MPZ mutations is also notable, because, in general, neither sympathetic nor parasympathetic nerves are myelinated. However parasympathetic fibers of the Edinger-Westphal nucleus are suggested to be thinly myelinated (15). For this reason, Adie’s pupil in patients with MPZ mutations could possibly be explained by a myelin defect. The mechanisms of other forms of parasympathetic autonomic dysfunction remain to be elucidated. To date, there have been no reports on sympathetic nerve dysfunction in patients with CMT2J. However, this case report revealed a possible partial impairment of the sympathetic nervous system, according to the HRV analysis findings (decreased LF/HF ratio), with no abnormalities in the SSR or MIBG cardiac scintigraphy. Furthermore, autonomic dysfunction has not been reported in CMT1B. Taken together, in CMT with MPZ gene mutations, parasympathetic dominant autonomic failure is the predominating clinical feature specific to CMT2J. The MPZ protein may therefore play a role in the autonomic nervous system, and the effect of the MPZ Thr124Met mutation needs to be further elucidated.

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

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