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【 CASE REPORT 】

A Sporadic Case of Charcot-Marie-Tooth Disease Type 2 with Left Vocal Fold Palsy due to Mitofusin 2 Mutation

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Abstract:

A 33-year-old Japanese woman was referred for hoarseness. She had been diagnosed with Charcot-Marie-Tooth disease at age 3 and bilateral optic atrophy at age 15. Laryngoscopy revealed left vocal fold palsy. These findings suggested Charcot-Marie-Tooth disease type 2; the diagnosis was confirmed by a mitofusin 2 mutation analysis. Her symptoms remained stable for almost 10 years. Although vocal fold palsy and optic atrophy have been previously reported in patients with mitofusin 2 mutations, detailed clinical information and clinical course have never been documented. These data might contribute to the elucidation of the pathological conditions associated with mitofusin 2 mutations.

Key words: Charcot-Marie-Tooth disease type 2, hereditary motor and sensory neuropathy, mitofusin 2, vocal fold palsy, optic atrophy, respiratory insufficiency

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Introduction

Vocal fold palsy is known to be a possible symptom of every type of Charcot-Marie-Tooth disease (CMT). It has been frequently reported in CMT type 2C (axonal type) due to mutations in the transient receptor potential vanilloid 4 (*TRPV4*) gene (1, 2). It is also expected in CMT type 1A (demyelinating type) (3) and CMT type 4A (intermediate type) due to mutations in the ganglioside-induced differentiation-associated protein 1 (*GDAP1*) gene (4). Mitofusin 2 (*MFN2*) has been reported to be the primary gene with mutations in CMT type 2A (5); in addition to vocal fold palsy, this mutation was associated with optic atrophy in a previous case series (6, 7).

We herein report the clinical course of a sporadic case of CMT type 2A with an *MFN2* mutation over a decade.

Case Report

A 33-year-old woman was referred to our hospital for hoarseness of unknown etiology. She had been diagnosed with CMT at age 3, which was initially based on gait disturbance. She developed decreased vision due to pointed atrophy of both optic nerves at age 15. Her distal extremities showed severe atrophy with pes cavus and weakness, but the proximal muscles were relatively well-preserved. The patient was wheelchair-bound but was able to maneuver it on her own. All tendon reflexes were absent. Superficial and vibratory perceptions were moderately decreased. Her visual acuity was 20/133 on the right side and 20/66 on the left side with bilateral central scotoma. Laryngoscopy revealed palsy of the left vocal fold as the cause of hoarseness. The left vestibular fold seemed to be atrophic on computed tomography (CT) (Figure). There were no lesions that might account for left recurrent laryngeal nerve palsy on chest CT. She did not complain of pain on swallowing during her course, and the curtain sign was absent. Brain magnetic resonance imaging revealed no indications of a proximal lesion of the left vagal nerve. These findings suggested that other potential causes of her vocal fold palsy, such as adventitious reactivation of varicella zoster virus, were unlikely. Her vital capacity was also reduced (48.3% of predicted). These findings suggested that neuropathy involved nerves other than extremities. Compound muscle action potentials were not evoked on routine nerve conduction studies, and the type of

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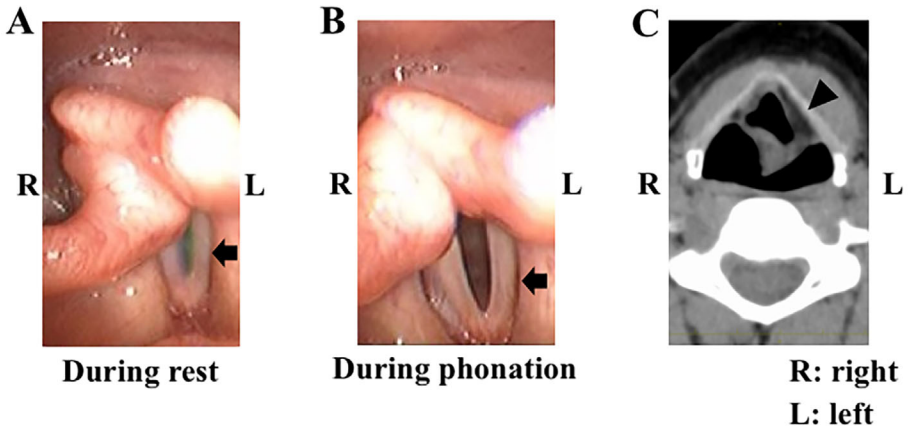

Figure. **The left vocal fold (arrows in A and B) did not adduct during phonation on laryngoscopic visualization. The left vestibular fold (arrowhead in C) had a lower density than the right vocal fold on computed tomography and seemed to be atrophic.**

CMT was not apparent. Her parents did not have consanguinity and were in good health with normal muscle strength, tendon reflexes, and sensory functions. Her younger sister was also healthy, and an inquiry survey revealed no similar patients in her family. Sporadic CMT accompanied by optic atrophy and vocal fold palsy was assumed. An *MFN2* analysis identified a mutation [c.1090C>T (p.Arg364Trp)] on exon 11.

Approximately 10 years after her genetic diagnosis, her condition was progressing at a considerably slow pace, with no marked difference in visual acuity, vocal fold palsy, or the respiratory or swallowing function.

Discussion

Six mutations in *MFN2* were subsequently reported as causative for CMT type 2A in seven pedigrees among patients of different races following the report of a mutation in kinesin family member 1B-β (5, 8). Various other mutations have been reported in succession (9, 10); these are considered to be the most common cause of the axonal type of CMT in Japan, accounting for almost 10% of cases (11, 12). CMT type 2A with the *MFN2* mutation has been described as common in patients who develop symptoms before age 10. Other patients with late onset have a propensity to progress slowly (10). The mode of inheritance and penetrance of *MFN2* mutations are uneven. Severity varies from asymptomatic to symptomatic among patients with the same mutation (9, 13). As with our patient who had unexplained early-onset severe distal weakness due to axonopathy, the *MFN2* mutation should be one of the most important responsible focuses that need to be explored first of all, even if the patient does not demonstrate any familial syndrome.

The laterality of the vocal fold palsy in our case might reflect the different lengths of the right and left recurrent laryngeal nerves. In other words, the longer the nerve, the more vulnerable it is in chronic degenerative types of CMT because *MFN2* might be involved in axonal transport of mitochondria (14). However, why her vocal fold palsy had been unilateral for a decade and whether or not the progression rate of the vocal fold palsy varies among patients with CMT remain unclear. In previous papers (2, 4), the severity showed a wide range, with some having unilateral disease and some requiring tracheostomy, but the long-term course of those patients, including those with CMT with the *MFN2* mutation, was not documented.

The optic atrophy in our patient was severe but remained stable over a decade, although the optic nerve degeneration associated with CMT has been reported to vary in previous case reports. For example, partial or full recovery with a subacute or sudden onset within a few hours has been described (6, 10, 15). It is difficult to illustrate hereditary chronic degeneration in such cases. Dominant optic atrophy is a known cause of optic atrophy, with optic atrophy 1 (*OPA1*) identified as the causative gene. Interestingly, both *MFN2* and *OPA1* are involved in the fusion of the mitochondrial membrane (14), and acute-onset or reversible visual impairment might be a consequence of mitochondrial dysfunction. Whether or not such syndromes due to *MFN2* mutations can be interpreted as mitochondrial disease remains a controversial topic (16-18). Nevertheless, it is crucial to treat such symptoms as mitochondrial disorders in these patients in order to understand the entire pathophysiology of *MFN2* mutations. In addition, the clinical course of symptoms, such as vocal fold palsy and optic atrophy, should be documented in more patients with an *MFN2* mutation for a longer period of time in order to accumulate more data.

The R364W mutation in our patient was assumed to affect the secondary structure of *MFN2* (19). This mutation has been associated with severe weakness of the extremities and other manifestations, such as vocal fold palsy and optic atrophy (6, 7, 12). In addition, respiratory insufficiency has also been documented (6), and the loss of her vital capacity may have been an asymptomatic manifestation. However, patients with the R364W mutation do not always have a se-

vere phenotype or manifestations other than axonal neuropathy; indeed, some have sporadic disease (7, 20). These reports suggest the diversity of pathophysiological mechanisms, even with a specific mutation, or that mild manifestations might be underappreciated in CMT type 2A with an *MFN2* mutation. The presence of manifestations other than axonal neuropathy should be a clue prompting physicians to suspect CMT type 2A with an *MFN2* mutation. Conversely, patients diagnosed with CMT type 2A and their relatives should be carefully examined for the presence of clinical manifestations other than axonopathy in order to elucidate the genotype-phenotype relationship.

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

References

1. Landouré G, Zdebik AA, Martinez TL, et al. Mutations in TRPV4 cause Charcot-Marie-Tooth disease type 2C. Nat Genet **42**: 170-174, 2010.
2. Chen DH, Sul Y, Weiss M, et al. CMT2C with vocal cord paresis associated with short stature and mutations in the TRPV4 gene. Neurology **75**: 1968-1975, 2010.
3. Thomas PK, Marques W Jr, Davis MB, et al. The phenotypic manifestations of chromosome 17p11.2 duplication. Brain **120**: 465-478, 1997.
4. Sevilla T, Jaijo T, Nauffal D, et al. Vocal cord paresis and diaphragmatic dysfunction are severe and frequent symptoms of GDAP1-associated neuropathy. Brain **131**: 3051-3061, 2008.
5. Züchner S, Mersiyanova IV, Muglia M, et al. Mutations in the mitochondrial GTPase mitofusin 2 cause Charcot-Marie-Tooth neuropathy type 2A. Nat Genet **36**: 449-451, 2004.
6. Züchner S, De Jonghe P, Jordanova A, et al. Axonal neuropathy with optic atrophy is caused by mutations in mitofusin 2. Ann Neurol **59**: 276-281, 2006.
7. Chung KW, Kim SB, Park KD, et al. Early onset severe and late-onset mild Charcot-Marie-Tooth disease with mitofusin 2 (MFN2) mutations. Brain **129**: 2103-2118, 2006.
8. Zhao C, Takita J, Tanaka Y, et al. Charcot-Marie-Tooth disease type 2A caused by mutation in a microtubule motor KIF1Bbeta. Cell **105**: 587-597, 2001.
9. Lawson VH, Graham BV, Flanigan KM. Clinical and electrophysiologic features of CMT2A with mutations in the mitofusin 2 gene. Neurology **65**: 197-204, 2005.
10. Verhoeven K, Claeys KG, Züchner S, et al. MFN2 mutation distribution and genotype/phenotype correlation in Charcot-Marie-Tooth type 2. Brain **129**: 2093-2102, 2006.
11. Abe A, Numakura C, Kijima K, et al. Molecular diagnosis and clinical onset of Charcot-Marie-Tooth disease in Japan. J Hum Genet **56**: 364-368, 2011.
12. Ando M, Hashiguchi A, Okamoto Y, et al. Clinical and genetic diversities of Charcot-Marie-Tooth disease with MFN2 mutations in a large case study. J Peripher Nerv Sys **22**: 191-199, 2017.
13. Muglia M, Vazza G, Patitucci A, et al. A novel founder mutation in the MFN2 gene associated with variable Charcot-Marie-Tooth type 2 phenotype in two families from Southern Italy. J Neurol Neurosurg Psychiatry **78**: 1286-1287, 2007.
14. Chandhok G, Lazarou M, Neumann B. Structure, function, and regulation of mitofusin-2 in health and disease. Biol Rev Camb Philos Soc **93**: 933-949, 2018.
15. Leonardi L, Marcotulli C, Storti E, et al. Acute optic neuropathy associated with a novel MFN2 mutation. J Neurol **262**: 1678-1680, 2015.
16. Iapadre G, Morana G, Vari MS, et al. A novel homozygous MFN2 mutation associated with severe and atypical CMT2 phenotype. Eur J Paediatr Neurol **22**: 563-567, 2018.
17. Finsterer J, Fiorini AC, Scorza CA, et al. CMT2 due to homozygous MFN2 variants is a multiorgan mitochondrial disorder. Eur J Paediatr Neurol **22**: 889-891, 2018.
18. Striano P, Iapadre G, Vari MS, et al. Multiorgan mitochondrial dysfunction is not a main feature of MFN2 mutations (Reply to: CMT2 due to homozygous MFN2 variants is a multiorgan mitochondrial disorder). Eur J Paediatr Neurol **22**: 892-893, 2018.
19. Calvo J, Funalot B, Ouvrier RA, et al. Genotype-phenotype correlations in Charcot-Marie-Tooth disease type 2 caused by mitofusin 2 mutations. Arch Neurol **66**: 1511-1516, 2009.
20. Feely SM, Laura M, Siskind CE, et al. MFN2 mutations cause severe phenotypes in most patients with CMT2A. Neurology **76**: 1690-1696, 2011.