INTERNAL MEDICINE

□ CASE REPORT □

Coenzyme Q10 Therapy in Hereditary Motor Sensory Neuropathy Type VI with Novel Mitofusin 2 Mutation

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Abstract

Hereditary motor sensory neuropathy type VI (HMSN VI) is hereditary neuropathy accompanied by optic neuropathy. The feasibility of Coenzyme Q10 (CoQ10) as a treatment for subacute visual impairment of HMSN VI was examined.

A 37-year-old patient with HMSN VI with a novel mitofusin 2 mutation was treated with high dose of CoQ10 (200 mg/day) for eight months.

Visual impairment was partially resolved after CoQ10 therapy.

High dose CoQ10 therapy may improve the prognosis of subacute visual impairment in HMSN VI. To confirm the effectiveness of CoQ10 on HMSN VI, further studies are needed.

Key words: MFN2, hereditary motor sensory neuropathy type VI, coenzyme Q10, polyneuropathy

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Introduction

Axonal Charcot-Marie-Tooth disease (CMT) with optic atrophy is referred to as hereditary motor and sensory neuropathy type VI (HMSN VI). Mutations in mitofusin 2 (MFN2) gene (*MFN2*) cause HMSN VI as well as CMT type 2A (1). MFN2 is an outer mitochondrial membrane protein, involved in mitochondrial fusion. MFN regulates mitochondrial metabolism, and loss-of-function reduces mitochondrial oxidative phosphorylization (2). MFN2 is also required for axonal mitochondrial transport and loss-of-function causes axonopathy. We report a novel mutation of *MFN2* (R364P) in a patient with HMSN VI and the effectiveness of oral coenzyme Q10 (CoQ10) therapy for subacute visual impairment in later life.

Case Report

A 37-year-old man, without any contributory family history, was referred to our hospital with subacute impairment of bilateral visual acuity. At age 22, he was diagnosed with CMT, because of slowly progressive muscle atrophy and weakness of distal extremities and steppage gait with onset at age 2. He was not able to walk without ankle-foot orthosis. On examination, he showed distal-dominant muscle atrophy and weakness of the upper and lower extremities (Fig. 1A), mild sensory disturbance in the distal extremities, and absence of deep tendon reflexes. On ophthalmologic examination, visual acuity was 20/200 on the left side and 20/500 on the right side. Bilateral optic atrophy was found upon opthalmoscopic examination (Fig. 1B). Humphry-Zeiss and Goldmann visual field examinations showed central scotomas on both sides (Fig. 2A). On electrophysiological study, compound muscle action potentials were markedly reduced or not evoked bilaterally, and no sensory nerve action potentials were evoked. Routine laboratory tests were normal.

After written consent was obtained from the patient, we analyzed all exons of *MFN2* by direct cycle sequencing, and demonstrated a G to C transversion at the second position of codon 364 on exon 11, which predicted a R364P substitution (Fig. 1C). We also searched for this mutation in 100 healthy Japanese, but none of them demonstrated this mutation. The patient did not have any disease-causing mutations in mitochondrial DNA.

We performed aerobic exercise test to assess his mitochondrial function. We measured the lactate and pyruvate

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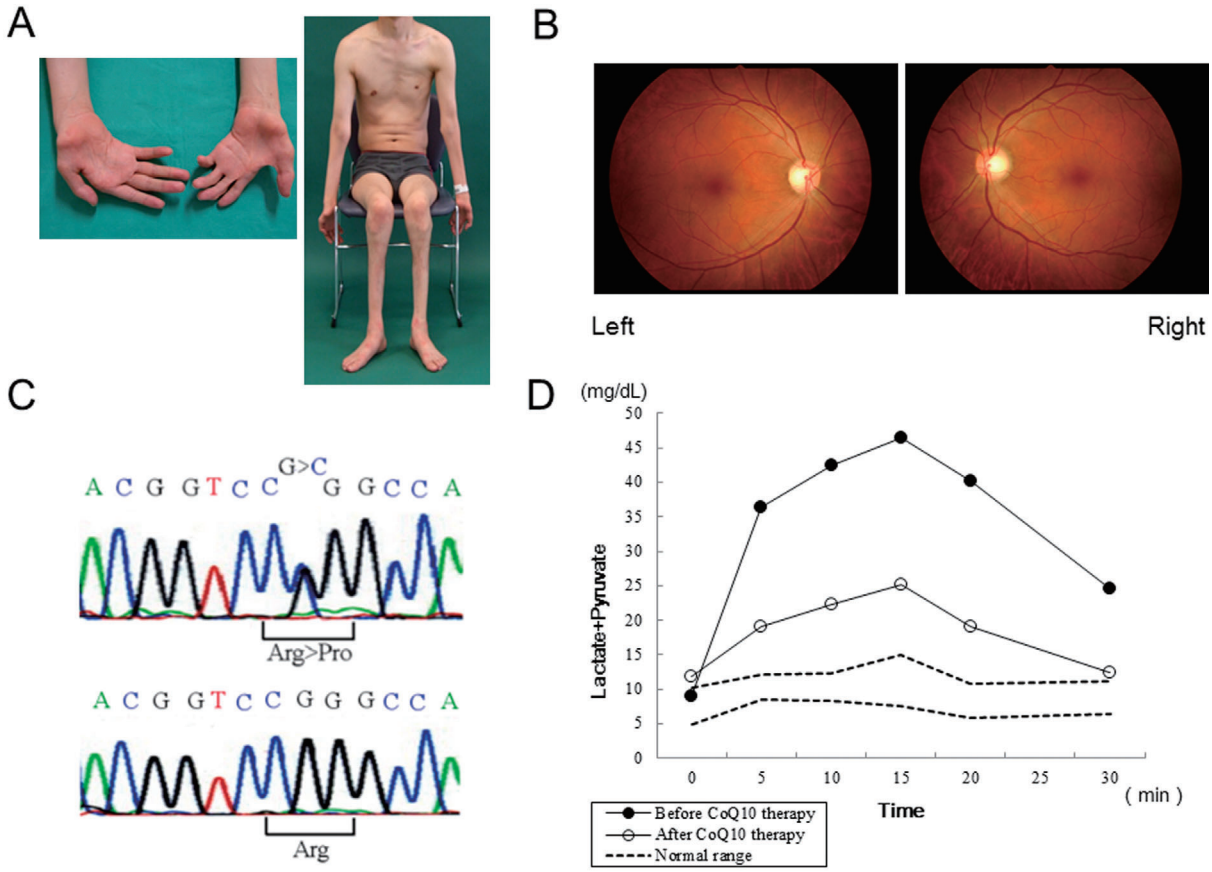

Figure 1. **Optic atrophy, gene mutation, and results of aerobic exercise test. A. The pictures of the present patient on admission. Note the prominent muscular wasting in the distal extremities. B. Bilateral optic atrophy upon opthalmoscopic examination. C. DNA sequence of exon 11 of the mitofusin 2 gene in the present patient (upper) and a control subject (lower). This patient showed a heterozygous G→C transversion at nucleotide position 1091, the second position of codon 364, leading to the substitution of Arg for Pro (R364P). D. Aerobic exercise test (15 Watt for 15 min). The ordinate indicates the blood lactate plus pyruvate level on aerobic exercise tests before and after CoQ10 therapy. The area between broken lines indicates mean ± 2SD of the control patients [Data are taken from (6)].**

levels before, during, after exercise on a bicycle ergometer (15 watt, 15 minutes) (3). The concentrations of serum lactate and pyruvate after aerobic exercise were significantly elevated compared to those before exercise, indicating mitochondrial dysfunction (Fig. 1D).

As some therapeutic benefits of CoQ10 have been reported in mitochondrial diseases (4), we started therapy with a high dose of oral CoQ10 (200 mg/day) for subacute visual impairment with the approval of the medical ethical committee and informed consent from our patient. He did not exercise while taking CoQ10 in order to exclude the effect of aerobic exercise training. Eight months after CoQ10 therapy was started, his vision had sufficiently improved so that he was able to read books without a magnifying glass, and the size of the central scotomas on Goldmann visual field examination became smaller than that before therapy (Fig. 2B). The elevation curves of lactate and pyruvate on exercise were decreased compared with those before therapy (Fig. 1D). Muscle weakness and sensory disturbance did not change, and there are no signs of improvement on the result of nerve conduction study after CoQ10 therapy.

Discussion

The present patient showed childhood-onset motor and sensory axonal neuropathy with adult-onset optic atrophy. With the diagnosis of HMSN VI, a novel *MFN2* mutation (R364P) was identified. A patient with a different mutation at the same codon (c. 1090 C>T, p. R364W) was reported with a different phenotype characterized by childhood-onset visual impairment with axonal neuropathy (1). The difference in the tertiary structure of MFN2 protein may differently affect the mitochondrial network architecture and function, leading to different clinical phenotypes. Importantly, visual impairment partially recovered after the initiation of CoQ10 therapy.

MFN2 deficiency represses nuclear-encoded subunits of OXPHOS (mitochondrial oxidative phosphorylation) complexes I, II, III, and V (2). The administration of CoQ10 may improve the activities of respiratory enzymes, espe-

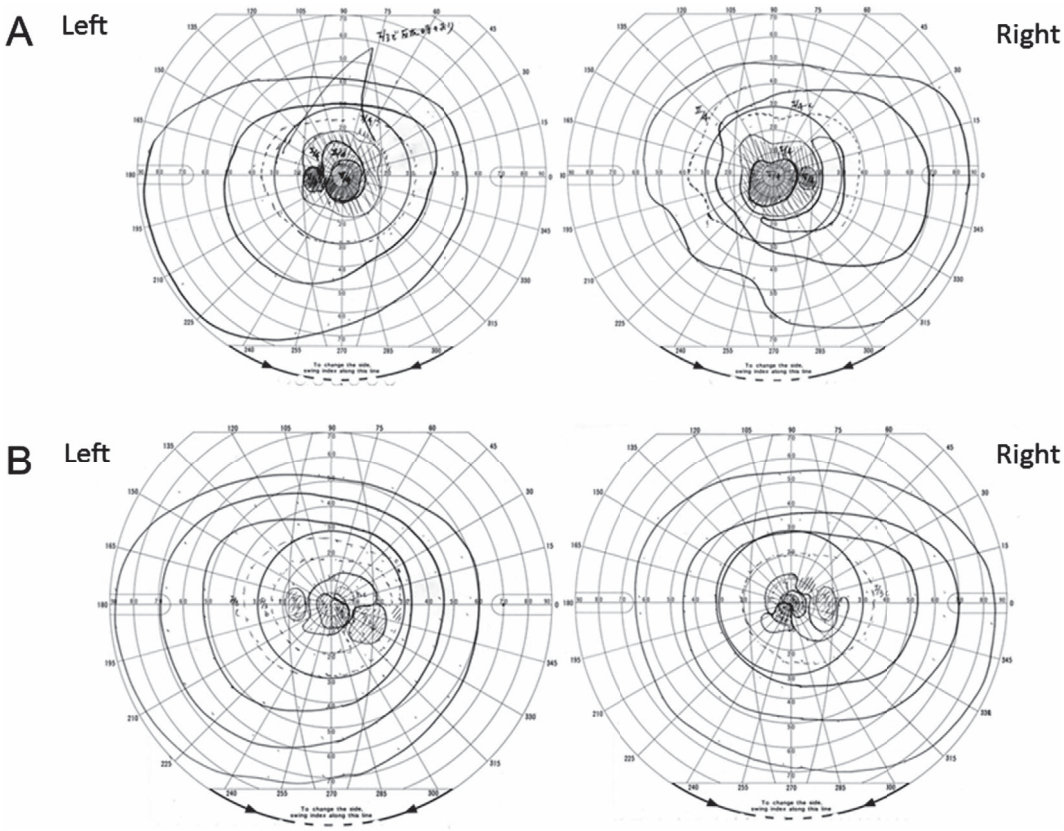

Figure 2. **The results of Goldmann visual field examinations before and after CoQ10 therapy. A. The visual field test showed bilateral central scotomas before CoQ10 therapy. B. The size of the bilateral central scotomas was reduced eight months after CoQ10 therapy.**

cially complex I and III of electron transport chains in mitochondria. CoQ10 levels in the human retina were reported to decline with age (5). The age-related decline in CoQ10 might impair mitochondrial energy generation in the patient's retina resulting in late onset visual impairment, whereas CoQ10 supplementation therapy might improve mitochondrial function leading to visual improvement. The improvement in serum lactate and pyruvate curves on aerobic exercise test after CoQ10 therapy suggests that CoQ10 would improve mitochondrial dysfunction caused by *MFN2* mutations. Although visual impairment may improve without medication in some patients with HMSN VI (1), the results of aerobic exercise test suggest the efficacy of CoQ10 therapy for subacute progression of visual impairment in HMSN VI.

Conclusion

In conclusion, we describe a patient with HMSN VI with a novel *MFN2* mutation. High dose CoQ10 therapy may improve the prognosis of subacute visual impairment in HMSN VI. These are only preliminary findings of HMSN VI treatment. A clinical trial of CoQ10 on a larger cohort of patients with MFN2 deficiency is needed.

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

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