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Structural and Functional Measures of Inner Retinal Integrity Following Visual Acuity Improvement in a Patient with Hereditary Motor and Sensory Neuropathy Type VI

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Abstract

Purpose—To report measures of inner retinal integrity following improvement in visual acuity and visual fields in a patient with hereditary motor and sensory neuropathy type VI (HMSN VI).

Case Report—The patient is a Caucasian male with HMSN VI (type 2A Charcot-Marie-Tooth disease and associated optic atrophy) and a c.1090C→T (p.R364W) mutation in the mitofusin 2 (*MFN2*) gene. The patient's best-corrected visual acuity improved from 20/200 (OD) and 20/400 (OS) at the initial visit to 20/25 in each eye when tested seven years later. The visual field defects in both eyes that were present at the initial visit were absent at the follow-up visit. The structural integrity of the inner retina was assessed by an evaluation of retinal nerve fiber layer thickness (RNFLT) using optical coherence tomography (OCT), and the functional integrity was assessed by the amplitude of the photopic negative response (PhNR) of the electroretinogram (ERG). At the follow-up visit, the patient's RNFLT was less than the 5th percentile for control subjects in the superior and inferior quadrants OD and in one sector of the temporal quadrant OS, but was within normal limits elsewhere. The PhNR amplitude of each eye was below the lower limit of the normal range.

Conclusion—The abnormally low PhNR amplitudes and abnormally thin RNFL in certain quadrants of the retina following improvement of visual acuity and visual fields to near-normal values illustrates the potential usefulness of assessing the structure and function of the inner retina in HMSN VI patients.

Keywords

Hereditary motor and sensory neuropathy; photopic negative response; OCT; ERG

Introduction

Hereditary motor and sensory neuropathy type VI (HMSN VI) is a severe form of Charcot-Marie-Tooth (CMT) disease type 2A with associated optic atrophy.^{1,2} CMT disease is a hereditary neuropathy that affects the peripheral motor and sensory nerves. CMT type 2A is an axonal form of the neuropathy that results in abnormal function of the peripheral axons.

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Disclosure of Interest

The authors report no conflict of interest.

In patients with CMT type 2A, the severity of axonal neuropathy and the age of onset can be variable. Some patients with CMT 2A have an early onset, severe axonal degeneration while other patients have a late onset, mild form of the disease. About 10–20% of individuals with the severe form also have associated optic atrophy, resulting in HMSN VI.³

HMSN VI is caused by mutations in the *MFN2* gene,^{1–4} which encodes a protein in the outer mitochondrial membrane. *MFN2* has an active role in mitochondrial fusion, is involved in the energy metabolism of the mitochondria, and is also found in the tethering sites of the mitochondria and the endoplasmic reticulum. Mutations in the *MFN2* gene result in axonal degeneration of the peripheral nerves, and in a subpopulation of patients, the sensory nerves are also affected.³

Axonal degeneration of the optic nerve in patients with HMSN VI results in optic atrophy and presents as pale optic discs on fundus examination. However, optic nerve involvement in patients with *MFN2* gene mutations has been variable. Züchner et al. reported ten individuals with *MFN2* gene mutations from six families; all ten individuals had optic nerve involvement (HMSN VI).⁴ Chung et al. reported nine individuals with *MFN2* gene mutations from four families; all nine of the affected individuals had a CMT type 2A phenotype, but only three individuals had associated optic nerve involvement (HMSN VI).²

Patients with HMSN VI most commonly have reduced visual acuity and central visual field defects. Some patients with HMSN VI have been reported to have regained near-normal visual acuity over the course of several years.^{2,4} Züchner et al. described ten patients with HMSN VI, two of whom regained near-normal visual acuity and four of whom showed partial improvement in visual acuity over several years.⁴ Chung et al. reported that two of their three patients with HMSN VI regained near-normal visual acuity.² Thus, there appears to be variability both in the severity of optic nerve involvement and in the potential for improvement in visual acuity in patients with HMSN VI. However, it is unclear whether the structure and function of the inner retina remain compromised in such patients.

Here we report measures of the structural and functional integrity of the inner retina following improvement in visual acuity and visual fields in a patient with HMSN VI due to a mutation in the *MFN2* gene. The structural integrity of the retinal nerve fiber layer (RNFL) was evaluated using spectral-domain optical coherence tomography (sd-OCT). The functional integrity of the inner retina was evaluated using the photopic negative response (PhNR) of the full-field flash electroretinogram (ERG). Diseases affecting the retinal ganglion cells, such as glaucoma and optic atrophy, have been shown to result in a reduced PhNR^{5,6}, and PhNR amplitude is reported to be correlated with RNFLT.⁷ To our knowledge, this is the first report of RNFLT and PhNR amplitude in an HMSN VI patient following visual acuity improvement.

Case Report

The patient is a Caucasian male of Italian ancestry who was diagnosed with CMT disease early in life and was monitored by a neurologist. He was referred to the Eye and Ear Infirmary (EEI), University of Illinois at Chicago, for an ophthalmic evaluation. The institutional review board at the University of Illinois at Chicago approved the test protocol and written informed consent was obtained from the patient and each control subject before testing.

The patient was 36 years old at the time of his initial visit to the electrophysiology clinic. At that visit, the patient reported blurred vision in both eyes. He stated that six months prior to the initial visit, he had noticed impaired vision in his left eye, and subsequently within three months, he had noticed that vision in his right eye had also worsened. He reported gradual

visual deterioration over the succeeding months. He also reported difficulty with color vision and photoaversion. A review of his family pedigree did not show any history of familial eye diseases.

A comprehensive ophthalmic evaluation was performed during the initial visit. The patient's best-corrected distance visual acuity was 20/200 OD and 20/400 OS. Color vision screening with the Ishihara plates showed a profound color vision defect. The patient was not able to identify any of the test plates. Goldmann kinetic perimetry was performed using the II2e and II4e test targets. The visual fields for the right and left eyes at this initial visit are presented in Figure 1a. The visual field of the left eye showed a central scotoma to the II4e target. The visual fields of both eyes showed partial ring scotomas to the II2e target and normal peripheral boundaries to the II4e test target.

Slitlamp examination of the anterior segment did not show any significant abnormalities. Ocular pressures were 14 mm Hg (OD) and 15 mm Hg (OS). There was no evidence of an afferent pupillary defect. Dilated fundus examination showed bilateral blurred disc margins nasally, and a few non-specific hypopigmentary changes. The peripheral retina and retinal vessels of each eye appeared normal. A fundus photograph of the left eye taken during the initial visit is shown in Figure 2. The findings from the fundus examination along with the associated visual acuity loss and visual field defects initially suggested Leber hereditary optic neuropathy (LHON).

Subsequent to his initial visit, DNA sequencing was performed. The test identified a variant in the *MFN2* gene: a transition from C to T in position 1090, which resulted in a R364W missense mutation. No other abnormal DNA sequence variants were identified in the coding sequence or in the intron/exon junctions of this gene. The presence of a mutation in the *MFN2* gene together with the visual symptoms confirmed the diagnosis of HMSN VI in this patient.

The patient returned for a follow-up visit approximately seven years after his initial visit. At this time, he had developed severe muscular involvement of his lower and upper extremities and was wheelchair-bound. His best-corrected distance visual acuity had improved to 20/25 OD and 20/25⁺¹ OS. Color vision screening showed that he could correctly identify the first three test plates in the Ishihara color vision test. The Goldmann visual field of the left eye lacked the central scotoma that was observed during the initial visit and the partial ring scotomas in both eyes were no longer found (Fig 1b). The peripheral boundaries remained normal to the II4e stimulus. Slitlamp and fundus findings were unchanged for both eyes between the initial and follow-up visits.

RNFLT measurements were obtained at the follow-up visit using sd-OCT (OPKO Instrumentation, Miami, FL). The peripapillary RNFL measurements were obtained for a 3.45-mm-diameter region centered on the optic nerve. The RNFL exam protocol used for scan acquisition automatically obtained three consecutive single scans, which were then averaged. This protocol was repeated three times for each eye to obtain three reproducible measurements of RNFLT. The RNFLT measurements were compared to normative data from 245 eyes of 123 visually normal subjects in the age range of 19 to 85 years (mean age, 43 years), provided by the manufacturer.

The OPKO software was used to calculate the RNFLT. The contour lines for the RNFLT measurement were determined by the system software. The thickness parameters evaluated were: average thickness (360 degrees), temporal quadrant thickness (316–45 degrees), superior quadrant thickness (46–135 degrees), nasal quadrant thickness (136–225 degrees), and inferior quadrant thickness (226–315 degrees). Each quadrant was further divided into

three smaller segments for analysis. The RNFL was considered abnormally thin if the value was less than the 5th percentile of the normative data.

Figure 3 shows the results of the sd-OCT scans of the RNFL. The superior and temporal quadrants of the right eye showed abnormal thinning of the RNFL, and the average value across all quadrants was below the 5th percentile. The left eye showed abnormal thinning in one segment of the superior quadrant, but the RNFLT was within normal limits for the other quadrants, as was the average value.

The PhNR was elicited using conventional stimulus parameters.^{7,8} A long-wavelength (640 nm) flash of 4-ms duration and luminance of 3 cd·s/m² was presented on a short-wavelength (464 nm) rod-saturating background with a luminance of 12.53 cd/m². Stimuli were generated by LED arrays and were presented in a ColorDome stimulator (Diagnosys LLC). A DTL electrode referenced to the forehead and a ground electrode attached to the ipsilateral earlobe were used to obtain the ERG recordings. Signals were acquired using an E² console (Diagnosys LLC).

ERG recordings were obtained from both eyes of the patient with HMSN VI and were compared with the recordings from one eye of each of ten visually normal control subjects, ages 22 to 61 years (mean age, 38 years). Pupils were dilated using 1% tropicamide and 2.5% phenylephrine hydrochloride drops. Subjects were adapted to the short-wavelength field for 3 minutes before the first stimulus was presented. Flash presentation was repeated with an inter-stimulus interval of 5 seconds until five recordings with minimal noise and eye movement artifacts were obtained. The mean of these five responses was used for analysis. Figure 4 presents the mean ERG response from the patient's right eye (solid trace) and left eye (dashed trace) together with the mean waveform for the control subjects (dotted trace).

PhNR amplitude was measured from the pre-stimulus baseline to the mean of the amplitude values between 60 and 80 ms following the flash. PhNR ratios were also calculated,⁹ defined as the ratio between the b-wave amplitude and the PhNR amplitude as measured from the b-wave peak to the mean of the amplitude values between 60 and 80 ms. In addition, a-wave amplitude was measured from the baseline to the a-wave trough, and b-wave amplitude was measured from the a-wave trough to the b-wave peak.

The a-wave, b-wave, and PhNR amplitudes obtained from the patient are presented in Table 1, together with the range of values obtained from the control subjects. The patient's a-wave and b-wave amplitudes were within normal limits. However, the PhNR amplitudes obtained from both eyes were below the range of normal values. In addition, the PhNR amplitude of the right eye was more reduced than that of the left eye. The PhNR ratios showed the same pattern of results (data not presented).

Discussion

In this report, we describe a patient with HMSN VI who had a R364W mutation in the *MFN2* gene and who showed a marked improvement in visual acuity to near-normal values in both eyes between the time of the initial visit and when examined seven years later. Visual fields also showed an improvement: the visual field defects recorded at the initial visit were absent on the follow-up visit. Even though visual acuity and visual field measures improved to near-normal values in this patient, measures of RNFLT and PhNR amplitude obtained at the follow-up visit were abnormal. Therefore, measures of visual acuity and visual fields obtained during the follow-up visit do not represent the extent of structural and functional impairment of the inner retina in this patient as reflected in the RNFLT and PhNR measurements.

Unlike the visual acuity and visual field measurements obtained on the follow-up visit, the RNFLT and PhNR amplitudes were asymmetric between the two eyes. Of interest, the eye with the worse visual acuity initially (OS) had less structural and functional abnormality of the inner retina following the visual acuity improvement. That is, the PhNR amplitude obtained from the right eye of the patient was smaller than that of the left eye, and the average RNFLT was less than the controls for the right eye but was within normal limits for the left eye.

Previous reports indicate that patients with a late onset of sub-acute visual loss, such as the patient in this report, often regain near-normal visual acuity after several years. However, patients who presented with an early onset of visual impairment and prolonged visual loss usually do not regain visual acuity.^{2,4} Thus, it might be useful to consider the age of onset and duration of visual symptoms as prognostic markers when counseling these patients about visual prognosis.

The mechanism of visual acuity improvement sometimes observed in patients with HMSN VI is unclear at present. Züchner et al. speculated that some nerve fiber bundles in the optic nerve might have a potential to regenerate over a prolonged time, thereby restoring near-normal visual acuity in these patients.⁴ However, the present results demonstrate that the structural and functional integrity of the inner retina can be compromised even in the presence of near-normal visual acuity and visual fields. Thus, RNFLT and PhNR amplitude measurements are potentially useful in assessing the structural and functional integrity of the inner retina in patients with HMSN VI.

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Figure 1.
Visual fields of the right and the left eyes recorded at the initial (1a) and follow-up (1b) visit.

Figure 2.
Fundus photograph of the left eye, taken during the initial visit, shows the hazy appearance of the optic disc margin.

Figure 3.

Cross sections of the OCT scans of the right (A) and left (C) eyes of the patient and the color-coded representation of RNFLT (μm) (green, greater than the 5th percentile; yellow, between the 5th and 1st percentiles; red, less than the 1st percentile of the control RNFLT) for the patient's right (B) and left (D) eyes. The blue lines in B and D represent the RNFLT of the patient's right and left eyes respectively. The numbers below the color-coded plots represent the RNFLT of the patient's right and left eyes corresponding to each of the 12 sectors.

Figure 4.

Mean ERG response of the patient's right eye (solid line), left eye (dashed line) and the mean waveform of control subjects (dotted line). The error bar represents the range of PhNR amplitudes for the control subjects. The line above the x-axis represents the duration over which the amplitude was averaged to obtain the PhNR amplitude for each subject.

Table 1

ERG amplitudes for the patient and control subjects

	a-wave amplitude	b-wave amplitude	PhNR amplitude
Patient OD	16.7 μ V	57.1 μ V	1.9 μ V
Patient OS	28.9 μ V	70.7 μ V	13.3 μ V
Control Range	11.6 – 52.4 μ V	13.8 – 118.7 μ V	22.1 – 63.6 μ V