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Macular Nerve Fibers Temporal to Fovea May Have a Greater Potential to Recover Function in Patients With Leber's Hereditary Optic Neuropathy

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Purpose: It is known that even after visual loss, younger patients with Leber's hereditary optic neuropathy (LHON) can recover vision. The purpose of this study was to determine the mean age at onset for LHON patients with and without visual recovery who carried the 11778 mutation, and to determine the pattern of central vision recovery.

Methods: Thirty-five LHON patients with the 11778 mutation of mitochondrial DNA who had visited the Keio University Hospital between 1980 and 1999 and were followed for 2 to 20 years, were the subjects of this retrospective study. The patients who had recovered vision were tested by Goldmann perimetry, Humphrey perimetry, and landmark-driven fundus microperimetry with a scanning laser ophthalmoscope (SLO). The fixation status was assessed by SLO microperimetry.

Results: Nine of the 35 patients (14 of 70 eyes) demonstrated a recovery of visual acuity to better than 0.3 in at least one eye. The mean age of disease onset was 15.9 ± 4.6 years in patients with visual recovery and 25.5 ± 8.9 years in patients without visual recovery. This difference in the mean age at onset was significant ($P = .0001$; Welch t-test). These 9 patients (14 eyes) showed fenestrated central scotomas in testing by Humphrey 10-2 threshold and SLO microperimetry. The nasal side of the central visual fields had a higher sensitivity than the temporal side in 7 of the 9 patients in Humphrey 10-2 threshold testing. Areas insensitive to 0 dB were detected on the nasal side of the central retina in these patients by SLO microperimetry, and fixation stability was related to the degree of clinical visual acuity.

Conclusion: The LHON patients with the 11778 mutation and a younger age of onset were more likely to show visual recovery. The findings made by perimetry suggest that the nerve fiber bundles in the nasal field (retina temporal to the fovea) may have a greater potential to recover function in LHON patients. **Jpn J Ophthalmol 2002;46:660–667**

Key Words: Fenestrated scotoma, Leber's hereditary optic neuropathy, 11778 mutation, SLO microperimetry, visual recovery.

Introduction

Leber's hereditary optic neuropathy (LHON) is a maternally transmitted eye disease in which the patient, usually a young man, shows an acute or subacute loss of central vision.[1] The loss of vision is generally severe and persistent, although some patients may show a gradual clearing of central vision or an opening of a few degrees within the central scotoma resulting in a form of "fenestrated scotoma."[2]

The most common mutations, which are significant risk factors for the development of LHON, have been found at one of three nucleotide positions, viz, 3460, 11778, or 14484, of the mitochondrial DNA (mtDNA) in the complex I subunit in more than 80% of LHON patients.[3] The major difference among the LHON patients with these three mtDNA mutations is the clinical outcome. There is a better visual prognosis in patients with the 3460 and 14484

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mutations than in those with the 11778 mutation. The 14484 mutation carries the best prognosis with visual recovery rates of 37% to 65%, while the 11778 mutation carries the worst prognosis with visual recovery rates of only 4–7%.[4–6]

There is a notable difference in the age of onset of the visual symptoms in patients with the 14484 mutation between those who regain vision and those who do not. The average age at onset for patients with visual recovery was 19.4 years, and 30.6 years for those who do not recover vision, as reported by Johns et al[7]; 17 years and 34 years in the report by Mackey and Howell[8]; and 16 years and 26 years in the report by Riordan-Eva et al.[5]

Patients with the 11778 mutation show a similar difference in some case reports with a lower teenage onset in those showing visual recovery.[2,9–14] Thus, recovery seems to be more likely when the visual deterioration begins at an early age, even in patients with the 11778 mutation.

In the present study, we first determined the mean age at onset for LHON patients with or without visual recovery who carried the 11778 mutation. Second, we examined the characteristics of the central vision in the LHON patients who showed visual recovery. Earlier studies used static perimetry to assess the visual function in LHON patients who exhibited recovery of vision,[9,15–20] and some of them showed a fenestration of the central scotoma. To confirm the sensitivity of the central retina and fixation status during perimetry, we performed examinations with Humphrey 10-2 threshold perimetry and scanning laser ophthalmoscope (SLO) microperimetry[21] in these patients with LHON.

Materials and Methods

Patients

Thirty-five Japanese LHON patients, who had visited the neuro-ophthalmology clinic of the Keio University Hospital between 1980 and 2000 and were followed for 2 to 20 years, were studied. All of these patients had the 11778 mutation of mtDNA confirmed by the gain of a restriction enzyme (*Mae*III) site of the polymerase chain reaction products, including nucleotide position 11778.[6] Their mean age at onset was 22.9 ± 9.2 years (10–45 years), and 30 were followed from the onset of visual decrease. Five of these 35 LHON patients visited our hospital with optic atrophy.

Since 1990, 10 of the 35 patients with LHON received idebenone (90–180 mg/day), riboflavin (60 mg/day), and ascorbic acid (750 mg/day) after giving their informed consent to use these medicines.[22,23] All medications were taken orally for about 1 year after the onset of the disease. Since 1994, 5 of these 10 patients also received 2 or 3 drops of isopropyl unoprostone (Rescula®; Fujisawa, Osaka) daily in each eye. This prostaglandin-related compound is used in treating glaucoma and has been shown to improve the circulation in the optic disc of animals.[24] Nine of these 10 patients recovered vision (Table 1).

Visual function following visual recovery was evaluated by determining the best-corrected visual acuity using the Landolt ring visual chart, Goldmann kinetic perimetric fields, the Humphrey 30-2 and 10-2 thresholds, and SLO microperimetry. Examinations of Goldmann and Humphrey perimetric fields were performed every 6 months after the initiation of visual recovery.

SLO Microperimetry

A confocal SLO (Rodenstock, Ottobrunn, Germany) with a static microperimetry program (Version 2.0.5) was used to test the 18 eyes of the 9 patients (cases 1 to 9) who had visual recovery (Table 1). The stimulus size was equivalent to the Goldmann III test spot. The duration of the stimulus was 0.1 seconds, and the 0 dB intensity was used to localize the scotomas. The intensity of the background illumination was 10 cd/m^2. A cross-shaped fixation target was used to determine the fixation point. Fixation was defined as stable if the patient fixated with a well-defined retinal locus; as relatively unstable if the preferred retinal locus changed but the point was within a 1.5° diameter circle; and as unsteady if it varied outside a 1.5° circle.[25]

Results

Age at Onset for Patients with Visual Recovery

Nine of the 35 patients, or 14 (20.0%) of 70 eyes, demonstrated a recovery of visual acuity to better than 0.3 in at least one eye (Table 1). The mean age of the disease onset was 15.9 ± 4.6 years in patients with visual recovery and 25.5 ± 8.9 years in patients without visual recovery. This difference in the mean age at onset was significant ($P = .0001$; Welch t-test).

Humphrey Perimetry

The Humphrey 10-2 threshold test was performed repeatedly after initiation of visual recovery in the right eye of case 5 that showed a gradual improvement of the nasal part of the central area of vision over a 16-month period (Figure 1). No fixation loss

Jpn J Ophthalmol
Vol 46: 660–667, 2002

Table 1. Nine Patients with Leber's Hereditary Optic Neuropathy who Showed Visual Recovery

Case No.	Sex	Age at Onset (y)	Medication	Family History	Visual Recovery*	Visual Acuity†		Goldmann Perimetry	SLO‡ Microperimetry Fixation Status
						Worst	Best		
1§	M	10	+	+	4/5	OD 0.07	1.0	Paracentral scotoma	Stable
						OS 0.08	1.0	Paracentral scotoma	Stable
2	M	10	−	+	1/3	N/A¶	1.0	Paracentral scotoma	Stable
						N/A	0.8	Paracentral scotoma	Stable
3	M	19	+	−	−	HM#	1.0	Paracentral scotoma	Stable
						0.07	0.09	Central scotoma	Unsteady
4‖	F	12	−	−	−	0.1	1.0	Cental scotoma	Stable
						0.1	0.8	Cental scotoma	Stable
5	M	14	+	−	−	0.04	1.0	Cental scotoma	Stable
						0.03	1.0	Cental scotoma	Stable
6§	M	16	+	+	4/5	0.01	1.0	Cental scotoma	Stable
						0.01	1.0	Cental scotoma	Stable
7	M	14	−	−	−	0.08	0.5	Cental scotoma	Relatively unstable
						CF**	0.06	Cental scotoma	Unsteady
8	M	17	+	−	−	0.07	0.3	Cental scotoma	Unsteady
						0.06	0.2	Cental scotoma	Unsteady
9	M	25	+	−	−	0.04	0.3	Cental scotoma	Relatively unstable
						0.02	0.06	Cental scotoma	Unsteady

*Number of patients with visual recovery ≥ 0.3 among affected patients with three generations in same family.
†The worst and best visual acuities during the course of follow-up.
§Same family.
‖Heteroplasic 11778 mutation.
¶His vision had deteriorated at the age of 10 years, but precise visual acuity was not available.
#Hand motion.
**Counting fingers.
‡SLO: scanning laser ophthalmoscope.

was observed in any of the tests. Goldmann perimetry as well as Humphrey perimetric 30-2 threshold test showed a central scotoma in the right eye of case 5, who achieved recovery of vision to 1.0 (Figure 2). However, the Humphrey perimetric 10-2 threshold test in case 5 showed a sensitive area in the nasal part of the central visual field with a fenestrated central scotoma.

The 9 patients, who achieved a visual recovery to better than 0.3, had areas of vision (cases 1–3), or fenestrations (cases 4–9) in the central scotoma in the Humphrey perimetric 10-2 threshold test (Figure 3, case 9 is not shown.). The former group showed paracentral scotomas and the latter group showed central scotomas in Goldmann perimetry (Table 1).

In 7 of the 9 patients (except cases 6 and 8) with visual recovery, the nasal part of the central visual field had a higher light sensitivity than the temporal field in Humphrey 10-2 threshold tests. The other 2 patients had central scotomas with some light-sensitive areas in the visual field just temporal (right eye of case 6 and left eye of case 8) to the center of vision. Although the Humphrey 10-2 threshold test could not detect the small island of sensitive area within the central scotoma in the left eye of case 6, SLO microperimetry was able to do so.[26]

SLO Microperimetry

The stability of fixation during perimetry was related to the visual acuity; the fixation was stable in 11 eyes with a visual acuity of 0.8 to 1.0, relatively unsteady in 2 eyes with a visual acuity of 0.3 and 0.5, and unsteady in 5 eyes with a visual acuity of less than 0.3 (Table 1, Figure 4).

SLO microperimetry detected sensitive and insensitive spots to 0 dB that coexisted in a pattern of paracentral scotomas or fenestrated central scotoma (spots sensitive to 0 dB surrounded by insensitive spots in the center of the retina). Spots sensitive to 0 dB were detected mainly in the temporal rather than the nasal part of the central retina in the eyes with visual recovery (Figure 4).

Discussion

It has been reported that the loss of vision in most LHON patients with a cecocentral scotoma and the 11778 mutation is profound and permanent.[4–6] How-

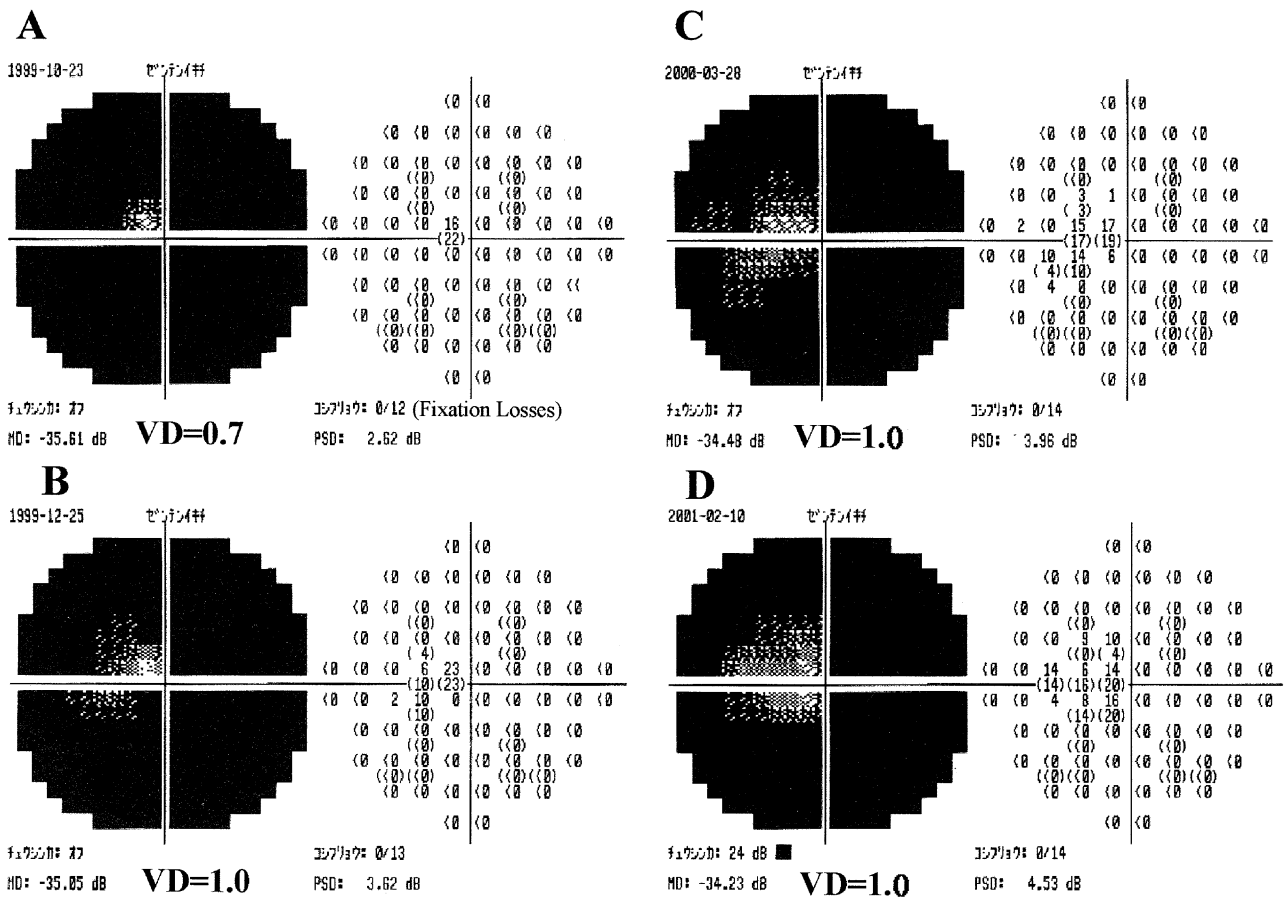

Figure 1. Humphrey 10-2 thresholds in the right eye of case 5 with Leber's hereditary optic neuropathy after the beginning of visual recovery. The fields show a gradual improvement in the fenestration of the central scotoma on the nasal side of the fixation. (**A**) 1999-10-23, (**B**) 1999-12-25, (**C**) 2000-3-28, and (**D**) 2001-2-10.

ever, some patients with this mutation have recovered excellent central vision even years after the initial visual deterioration.[2,9–14] Such patients may experience improvement of over a few central degrees, resulting in a small island of vision within a central scotoma, a form of fenestrated scotoma. Our LHON patients who recovered visual acuity of up to 1.0 showed either a paracentral scotoma or a fenestrated scotoma, with the former showing a better form of visual recovery than the latter.[8,9,17]

Interestingly, the Humphrey 10-2 threshold test showed that the nasal part of the central visual field (or the retina temporal to the macular) had greater light sensitivity than the temporal visual field (or the retina nasal to the macula) in eyes with visual recovery. Similar findings have been reported with the Humphrey threshold test in a patient with the 11778 mutation and visual recovery,[9,18] as well as in a patient with the 14484 mutation and visual recovery.[8,16,19,20] Thus, this finding may be characteristic of the process of visual improvement in LHON patients. A similar field defect, mimicking a bitemporal field defect obtained by kinetic perimetry, has previously been reported in 2 patients from one family with LHON.[27]

The newly developed SLO static microperimetry makes controlled fundus perimetry possible. This method of landmark-driven fundus perimetry eliminates the problem of unsteady fixation and alignment that is associated with conventional static perimetry.[21] Therefore, this method can be used to confirm the fixation point and the local sensitivity in the central retina during perimetry. In this study, spots insensitive to 0 dB were predominantly detected on the nasal side of the central retina in the LHON patients with visual recovery. This finding is compatible with that of the Humphrey 10-2 threshold test in 7 of the 9 patients with visual recovery in this study. Mackey[16] reported

Jpn J Ophthalmol
Vol 46: 660–667, 2002

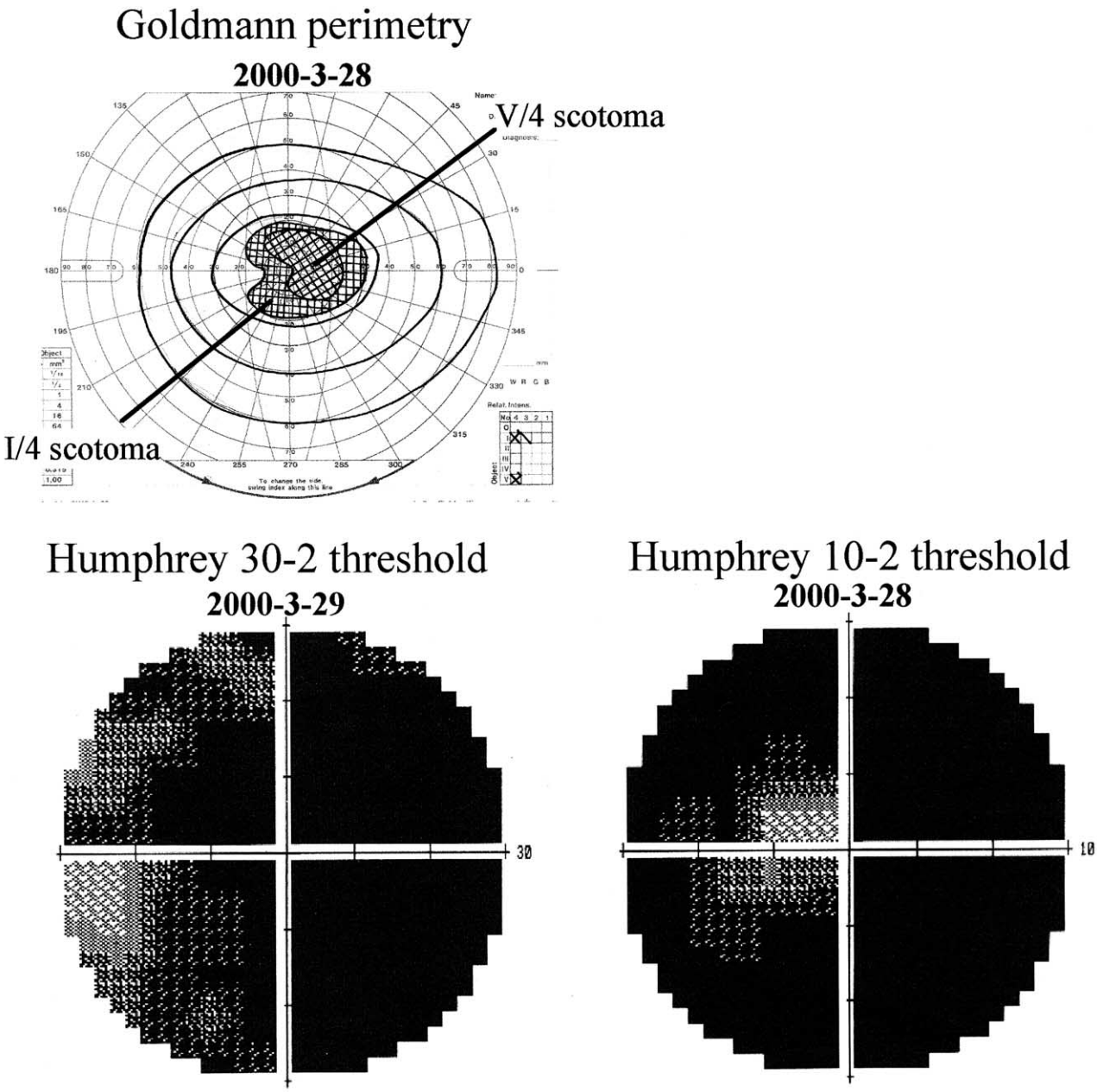

Figure 2. Results of Goldmann kinetic perimetry, Humphrey 30-2, and 10-2 thresholds in the right eye of case 5 with Leber's hereditary optic neuropathy. The fenestration of the central scotoma is more evident in the central 10° threshold perimetry.

an LHON patient with the 11778 mutation who recovered vision to 6/6 and had such a small island of vision within the central scotoma that it could not be detected on any type of conventional visual field examination. However, SLO microperimetry could detect the sensitive spot within the central scotoma in a similar patient with LHON in the present study, in the left eye of case 6.[26]

We found that the stability of fixation during perimetry was correlated with the clinical visual acuity. Eleven eyes with a visual acuity of 0.8 to 1.0 showed stable fixation. Thus, results of the Humphrey 10-2 threshold tests were reliable because of stable fixation. On the other hand, the 2 eyes in case 8 with visual acuity of 0.2 and 0.3 showed an unsteady fixation with fixation points covering a broad paramac-

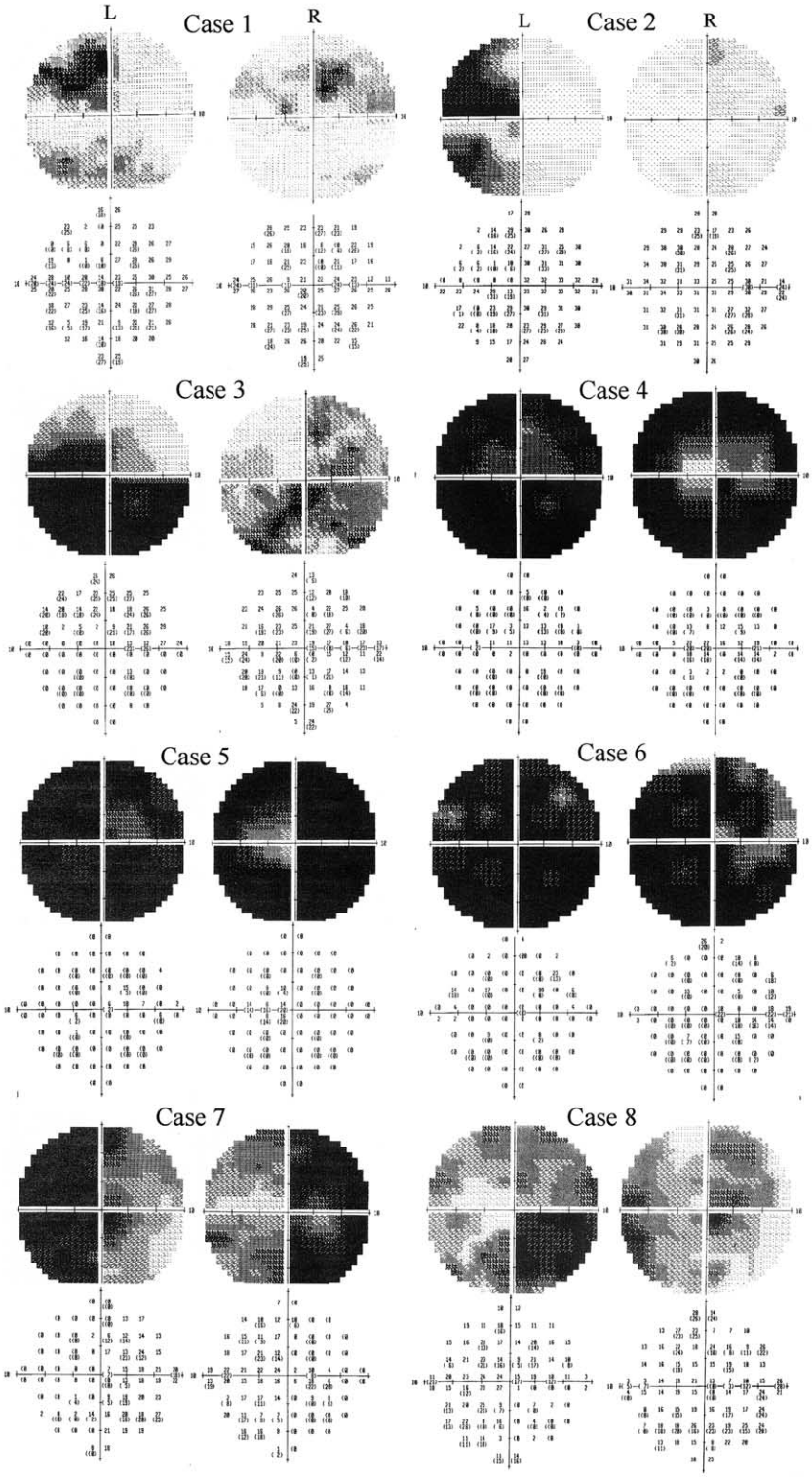

Figure 3. Humphrey 10-2 threshold test results shown in 8 patients with Leber's hereditary optic neuropathy who showed visual recovery. The fields show greater light sensitivity on the nasal part of the central visual field than on the temporal side, except in cases 6 and 8.

Jpn J Ophthalmol
Vol 46: 660–667, 2002

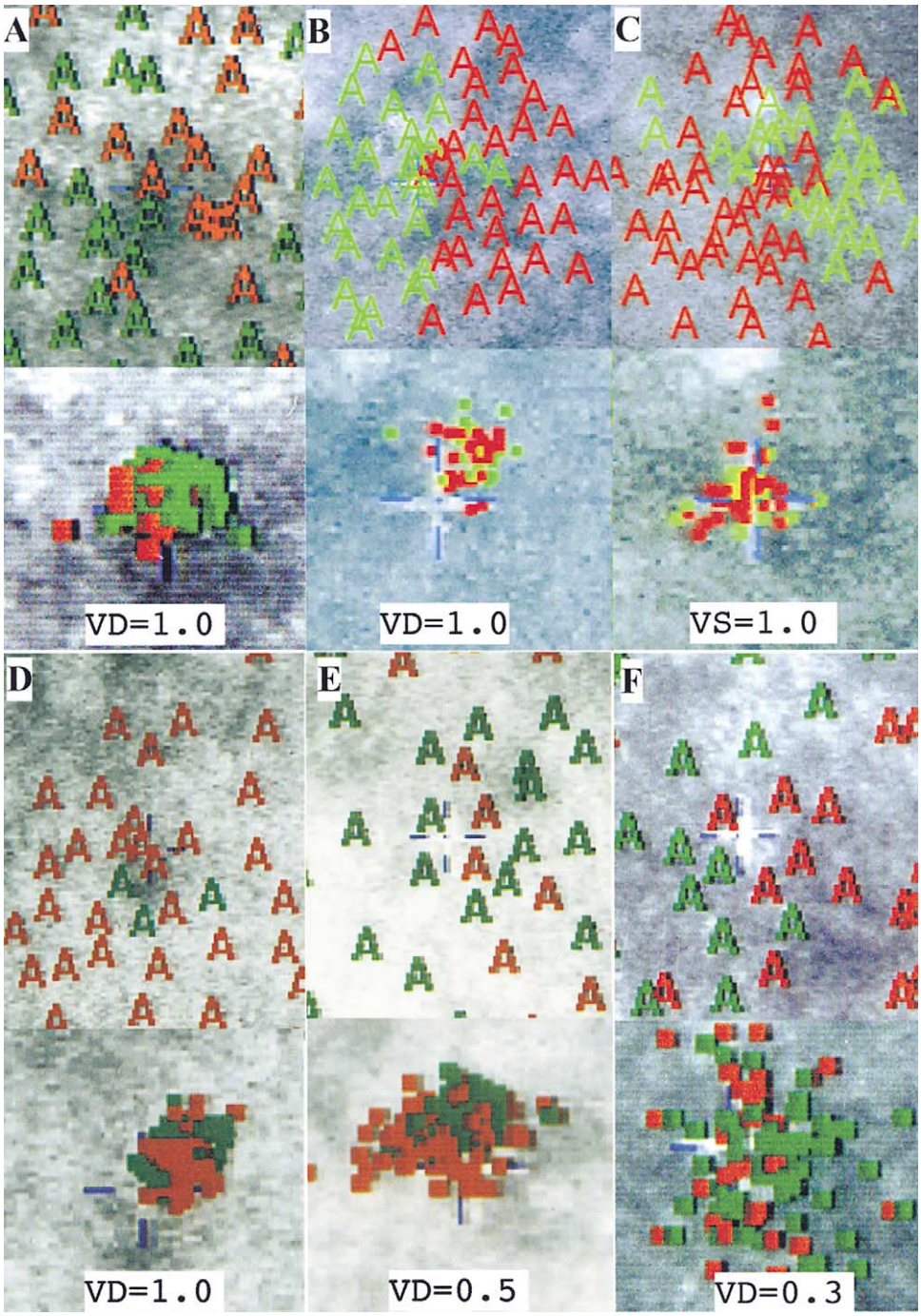

Figure 4. Results of scanning laser ophthalmoscope microperimetry (upper) and fixation status (lower) tests in patients with Leber's hereditary optic neuropathy who showed visual recovery. The blue cross indicates the last fixation spot in the examination. The green letter A indicates points seen by the patient, while the red letter A indicates the points not seen. (**A**) Case 3, right eye; (**B**) case 5, right eye; (**C**) case 5, left eye; (**D**) case 6, right eye; (**E**) case 7, right eye; (**F**) case 8, right eye. Fixation is stable in (**A**) to (**D**), relatively unstable in (**E**), and unsteady in (**F**).

ular area. Thus, the results of the Humphrey 10-2 threshold test in case 8 may not be reliable. However, SLO microperimetry in the right eye of case 8 (Figure 4F) demonstrated better sensitivity in the temporal side of the central retina than in the nasal, which is compatible with the result of the Humphrey 10-2 threshold test.

The pattern of visual improvement in our LHON patients would suggest that the nerve fiber bundles on the temporal side of the fovea might have greater potential to recover function after the onset of LHON than those on the nasal side. The dendritic fields of midget and parasol ganglion cells in the nasal quadrant are smaller than those of cells in the temporal, upper, and lower quadrants, because the spatial density of those ganglion cells is higher in the nasal quadrant.[28] This retinal asymmetry in the central vision might be associated with the visual recovery pattern of the disease.

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