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Do Idebenone and Vitamin Therapy Shorten the Time to Achieve Visual Recovery in Leber Hereditary Optic Neuropathy?

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Objectives: The authors investigated the effectiveness of idebenone combined with vitamin B_2 and vitamin C in the treatment of patients with Leber hereditary optic neuropathy (LHON) in an early stage as compared with untreated patients with LHON. These agents may stimulate the formation of ATP.
Materials and Methods: For this retrospective study, the authors selected 28 outpatients with LHON from the Keio University Hospital. These patients were followed for 2 to 19 years from disease onset. They were divided into two groups: 14 untreated patients (11778 mutation in 10 patients, 3460 mutation in 2 patients, and 14484 mutation in 2 two patients); and 14 treated patients (11778 mutation in 11 patients, 3460 mutation in 1 patient, and 14484 mutation in 2 patients). The treated patients were administered medical treatment with idebenone, vitamin B2, and vitamin C for at least 1 year. The current study evaluated the following: 1) number of eyes with visual recovery ≥ 0.3; 2) interval between the onset of LHON and the beginning of visual recovery; 3) interval between the onset of LHON and visual recovery to 0.3; and 4) interval between the beginning of medical treatment and the beginning of visual recovery in the treated subjects.
Results: There was no significant difference in the number of eyes with visual recovery ≥ 0.3 in the two groups with the 3460, 11778, or 14484 mutation. Patients with visual recovery showed a fenestrated scotoma or a clearing of central vision. The mean interval between the onset of LHON and the beginning of visual recovery was significantly shorter in the treated group (11.1 months) than in the untreated group (17.4 months) ($P = 0.03$). The mean interval between the onset of LHON and visual recovery to 0.3 was significantly shorter in the treated group (17.6 months) than in the untreated group (34.4 months) ($P = 0.01$). The mean interval between the initiation of medical treatment to the beginning of visual recovery was 5.4 months.
Conclusions: Results suggest that the administration of idebenone, vitamin B2, and vitamin C sped the recovery of vision in patients with LHON.
Key Words: Idebenone—Leber hereditary optic neuropathy—Visual recovery—Vitamin B2—Vitamin C.

Leber hereditary optic neuropathy (LHON) is a maternally inherited eye disease in which the patient, usually a young man, has an acute or subacute loss of central vision. The loss of vision is generally severe and persistent, although some patients have demonstrated an improvement in vision with time (1). Primary mutations, which are significant risk factors for the development of LHON, have been found at one of three nucleotide positions of the mitochondrial DNA (3460, 11778, or 14484) in a complex I subunit in more than 80% of the patients with LHON (2–4). The major difference among the patients with LHON with these three mitochondrial DNA mutations is the clinical outcome. The 11778 mutation carries the worst prognosis, with visual recovery rates of 4% to 7% (5,8–10). The 14484 mutation carries the best prognosis, with visual recovery rates as high as 50% (7–10). Visual recovery of patients with LHON with the 3460 mutation shows an intermediate frequency (6,8–10).

In 1992, we reported the results of treatment with idebenone (Takeda Chemical Industries, Osaka, Japan), a quinol compound that may contribute to stimulation of the formation of ATP (11), in a 10-year-old Japanese boy with LHON and the homoplasmic 11778 mutation (12,13). Four to 7 months after the initiation of treatment, he recovered visual acuity OU to 1.2 in association with fenestrated scotomas. We then treated additional patients with LHON after an acute onset of visual loss with administration of idebenone, vitamin B_2, and vitamin C. The plasma level of flavin mononucleotide, an activated form of vitamin B_2, is reportedly reduced in patients with LHON (14). Vitamin B_2 functions as a cofactor for electron transport in complex I and complex II (15). Interestingly, a patient with mitochondrial myopathy and a complex I dysfunction was successfully treated with 100

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mg/d vitamin B_2 (16). Vitamin K has been administered in combination with vitamin C in an attempt to donate electrons directly to cytochrome *c* (15). The use of vitamin C to protect against the damage caused by hydroxyl free radicals has been evaluated (17).

The current retrospective study reports the visual outcome in patients with LHON after treatment with idebenone, vitamin B_2, and vitamin C as compared with that in untreated patients with this disorder.

PATIENTS AND METHODS

Twenty-eight Japanese patients with LHON who had visited the neuroophthalmology clinic of the Keio University Hospital within 10 months of disease onset, between 1980 and 1995, were selected for this study. The patients were followed for 2 to 19 years. Since 1990, 14 patients with LHON gave informed consent to receive idebenone (180 mg/d), riboflavin (60 mg/d), and ascorbic acid (750 mg/d), all administered orally. Since 1994, 8 of the 14 patients also were administered eye drops that contained isopropyl unoprostone (Rescula; Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan), two drops daily OU. This prostaglandin-related compound is used for treatment of glaucoma, and it has been shown to improve the circulation in the optic disc of animals (18,19).

The 28 patients with LHON were divided into two groups: untreated patients (n = 14; group 1) and treated patients (n = 14; group 2). Group 1 consisted of 13 males and 1 female (mean age at onset, 23.6 ± 8.2 years; range, 14–41) who visited our hospital before 1990. Ten patients in group 1 had the 11778 mutation, two patients had the 3460 mutation, and two patients had the 14484 mutation. Group 2 consisted of 12 males and 2 females (mean age at onset, 23.1 ± 8.9 years; range, 17–45) who visited our hospital since 1990 and were administered medical therapy for at least 1 year. Eleven patients in group 2 had the 11778 mutation, one patient had the 3460 mutation, and two patients had the 14484 mutation. The interval between the onset of LHON and the administration of medical treatment in group 2 ranged from 2 to 9 months. During follow-up in all 28 patients, the worst visual acuity was below 0.1 and associated with dense cecocentral scotomas.

Visual function was evaluated by testing the subject's best-corrected visual acuity and by Goldmann kinetic perimetry and Humphry static perimetry. The current study retrospectively evaluated the following: 1) number of eyes with visual recovery equal to or greater than 0.3; 2) interval between the onset of LHON and the beginning of visual recovery; 3) interval between the onset of LHON and visual recovery to 0.3; and 4) interval between the beginning of medical treatment and the beginning of visual recovery in the treated subjects (group 2).

Statistical Methods

Differences in the number of eyes with visual recovery in each group were evaluated according to the mutation present using the Fisher exact probability test. Differences between intervals were analyzed by the Mann-Whitney U test. A level of $P < 0.05$ was considered statistically significant.

RESULTS

The number of eyes in each group that achieved a visual recovery ≥0.3 is shown in Table 1. Outcome also was evaluated according to the mutation present. Overall, the patients in each group with the 3460, 11778, or 14484 mutation showed no significant difference in outcome. The patients with a visual recovery ≥0.3 showed a central scotoma with fenestration or a clearing of central vision, seen with Humphry static perimetry, or they had paracentral scotomas, seen with Goldmann kinetic perimetry. In contrast, patients who did not achieve visual recovery showed dense central scotomas on either type of perimetric testing.

Data regarding the four patients in group 1 (cases 1–4) who had a visual recovery ≥0.3 and the six patients in group 2 (cases 5–10, with the three primary LHON mutations) who had a visual recovery are shown in Table 2. The two groups showed no difference in age at which LHON developed. The mean interval between the onset of LHON and the beginning of visual recovery was 17.4 months in group 1 and 11.1 months in group 2; this interval was significantly shorter in group 2 ($P = 0.03$). The mean interval between the onset of LHON and visual recovery to 0.3 was 34.4 months in group 1 and 17.6 months in group 2; this interval was significantly shorter in group 2 ($P = 0.01$). In group 2, the mean interval between the beginning of medical treatment and the beginning of visual recovery was 5.4 months. Four of the eight patients (cases 7–10) who were administered topical isopropyl unoprostone in addition to the oral medications showed a recovery of vision ≥0.3.

DISCUSSION

Some of the manifestations of mitochondrial disease may respond to treatment with agents that increase mitochondrial energy production (15). These agents include the naturally occurring cofactors involved in mitochondrial metabolism, such as coenzyme Q_{10}, succinate, vitamin K1 or vitamin K3, in conjunction with vitamin C, thiamine, and vitamin B_2 (1,15). Previously, we reported attempts to treat patients with LHON with oral idebenone (12,13). This agent, a quinol, may stimulate the formation of ATP in the cerebrum (11) and may inhibit

TABLE 1. *Number of eyes with visual recovery ≥0.3 associated with three primary Leber hereditary optic neuropathy mutations*

Genotype	Group 1 (n = 28 eyes) (% untreated)	Group 2 (n = 28 eyes) (% treated)	*P* value*
3460 mutation	2/4 (50)	1/2 (50)	0.80
11778 mutation	1/20 (5)	6/22 (27)	0.06
14484 mutation	4/4 (100)	2/4 (50)	0.21

* Fisher exact probability test.

TABLE 2. *Course of ten patients with Leber hereditary optic neuropathy (LHON) who achieved a visual recovery ≥0.3*

Group	Case	Sex	Age (yr) at onset (mean ± SD)	Eye	Genotype	Visual acuity		Humphry perimetry, final	Interval (months)			
						Worst	Final		Between onset of LHON to treatment	Between treatment and beginning of visual recovery (mean ± SD)	Between onset of LHON to beginning of visual recovery (mean ± SD)	Between onset of LHON to 0.3 (mean ± SD)
1 (Untreated)	1	M	14	R	3460	0.01	1.0	Fenestrated scotoma	–	–	14	46
				L		0.01	0.7	Fenestrated scotoma	–	–	13	48
	2	M	11	R	11778	0.05	0.5	Fenestrated scotoma	–	–	24	48
				L		FC*	0.03	Central scotoma	–	–	–	–
	3	M	24	R	14484	0.1	1.2	Clearing of central vision	–	–	12	17
				L		0.01	1.2	Clearing of central vision	–	–	12	19
	4	M	28	R	14484	0.05	0.7	Clearing of central vision	–	–	25	37
				L		0.05	0.5	Fenestrated scotoma	–	–	22	26
			(19.3 ± 8.1)								(17.4 ± 5.9)	(34.4 ± 13.7)
2 (Treated)	5	M	23	R	3460	0.01	0.08	Central scotoma	9	–	–	–
				L		0.01	0.4	Fenestrated scotoma	9	3	13	22
	6	M	10	R	11778	0.08	1.2	Fenestrated scotoma	8	1	9	10
				L		0.08	1.2	Fenestrated scotoma	8	2	10	11
	7	M	20	R	11778	HM†	1.0	Fenestrated scotoma	2	10	12	15
				L		0.07	0.08	Central scotoma	2	–	–	–
	8	M	25	R	11778	0.04	0.6	Fenestrated scotoma	2	12	14	24
				L		0.02	0.1	Central scotoma	2	–	–	–
	9	M	16	R	11778	0.07	0.4	Fenestrated scotoma	5	3	8	26
				L		0.06	0.3	Fenestrated scotoma	9	12	21	33
	10	M	18	R	14484	0.1	0.4	Clearing of central vision	3	3	6	8
				L		0.03	0.6	Clearing of central vision	3	3	6	9
			(18.7 ± 5.4)							(5.4 ± 4.5)	(11.1 ± 4.8)	(17.6 ± 9.0)

$P = 0.03$‡ $P = 0.01$‡

* Finger count.
† Hand motion.
‡ Mann-Whitney U test.
L, left; R, right.

lipid peroxidation in the mitochondrial membrane (20). Lipid peroxidation blockers may inhibit the death of retinal ganglion cells induced by inhibition of oxidative phosphorylation and glycolysis (21). In the rat, idebenone readily enters the brain and becomes localized in the mitochondria (22). In evaluating the visual response to idebenone in patients with LHON, the possibility of a spontaneous recovery of vision hampers the ability to objectively evaluate the effectiveness of drug therapy. Therefore, we are uncertain as to whether idebenone administered in combination with vitamin B2 and vitamin C may have improved the visual recovery of patients with early-stage LHON. However, the mean interval between the onset of LHON and the beginning of visual recovery, and the mean interval between the onset of LHON and the recovery of vision to 0.3, were both significantly shorter in the treated patients compared with the untreated patients. It is possible that such treatment accelerated or promoted visual recovery in those patients with a potential for a spontaneous recovery of vision. These agents could therefore accelerate the patients' visual recovery after onset of the disease. Patients with LHON who experience a recovery of vision reportedly exhibit a few degrees of opening of the central scotoma; a form of fenestrated scotoma develops (23–26). In the current study, patients with a visual recovery ≥0.3

showed central scotoma with fenestration or clearing of central vision, seen with Humphry static perimetry. Their visual recovery was associated with the appearance of a sensitive area in the central vision.

The effectiveness of mega-doses of idebenone (270 mg/d) administered in combination with vitamin B_{12} (5,000 IU/d) was reported in the case of a North African patient with LHON with the 14484 mutation (26). Six months after onset (3 months after the start of therapy), his visual acuity improved to 20/25 OD and 20/30 OS. This patient's abnormally elevated level of serum lactate returned to the normal range after 3.5 months of therapy. The authors concluded that treatment with idebenone and vitamin B_{12} may accelerate or promote visual recovery and improve the bioenergic condition of muscle in this disease (26). In another case report, a 15-year-old Japanese boy with the 11778 mutation had improved visual acuity OD from 0.1 to 0.5 3 months after disease onset and 1 month after administration of idebenone and vitamin B_2 (27). Mega-doses of idebenone (135 or 405 mg/d) were reported to be effective for treatment of spastic paraparesis in a patient with LHON (28).

The optic neuropathy in LHON is caused by the degeneration of the retinal ganglion cells and optic nerve axons (29). Neuropathologic studies show a degeneration of the ganglion cell layer and the optic nerve in the absence of marked inflammation (30–32). The loss of vision in LHON is because of the specific degeneration of the ganglion cell layer that is mainly associated with the papillomacular bundle. Howell (29) hypothesized that the respiratory chain dysfunction because of primary LHON mutations leads to axoplasmic stasis and swelling that blocks the function of the ganglion cells and causes a loss of vision in the acute stage. In most cases of LHON, these inactive ganglion cells die, probably via an apoptotic pathway. However, some inactive ganglion cells may remain viable for a long time. Howell (29) termed such ganglion cells "viable-but-inactive neurons" that may be associated with the recovery of vision in LHON.

In patients with LHON who achieved a visual recovery, such viable-but-inactive neurons may harbor normal or heteroplasmic mitochondrial DNA with a small amount of the primary mutation because when visual recovery does occur, it remains unchanged without recurrence (1). Optic neurons with homoplasmic normal mitochondrial DNA may show no further respiratory chain dysfunction. One explanation for the possible effectiveness of idebenone combined with vitamins B_2 and C is to stimulate the formation of ATP in the viable-but-inactive ganglion cells and to inhibit lipid peroxidation in the mitochondria of these cells. Further studies regarding the effectiveness of mega-doses of idebenone administered in combination with vitamins B_2 and C in a large number of patients in a relatively early stage of LHON are indicated.

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Addendum: Idebenone is now available in only two countries, Italy and Argentina.