Preservation of Photic Blink Reflex in Leber’s Hereditary Optic Neuropathy

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Purpose. To examine whether the early response of photic blink reflex (PBR) is spared in patients with Leber’s hereditary optic neuropathy (LHON).

Methods. Twenty-six patients with bilateral optic neuropathy (visual acuity \(\leq 0.1\)) and central scotomata were divided into LHON group with one of three mitochondrial DNA mutations at nucleotide position of 3460, 11778, or 14484 and non-LHON group without them. Latencies of the PBR early response and those of the electrically evoked blink reflex (EBR) response were compared among the 26 patients and 20 healthy volunteers.

Results. In controls, average latency of the PBR response was 50.3 ± 2.4 msec and was in accordance with previous reports. Ten of eleven patients with LHON had normal PBR responses, whereas 12 of 15 controls without LHON had abnormal responses \((P = 0.0005)\). Latencies of EBR responses were normal in all but one patient with LHON.

Conclusions. The afferent fibers of the PBR early response, as well as those of the light reaction, are reported to terminate presumably in the pretectum. Together with the reported evidence of the preserved light reaction in patients with LHON, we presume that W retinal ganglion cells may project common afferent fibers of these two neuronal pathways and may be preferentially spared in patients with LHON. Invest Ophthalmol Vis Sci. 1996;37:2736-2743.

Leber’s hereditary optic neuropathy (LHON) is a bilateral optic atrophy with acute or subacute onset that primarily affects young men. Several mitochondrial (mt) DNA mutations associated with LHON have been identified, which can account for the unique maternal transmission trait of LHON. Detection of the mtDNA mutations has facilitated the diagnosis of LHON, especially for sporadic cases of bilateral optic neuropathy whose causes could not be determined by traditional examination. On the other hand, the pathogenesis of LHON is still unclear. In our previous work, 10 of 18 patients with bilateral optic neuropathy were found to have the mtDNA mutations specific for LHON. Their clinical findings were so similar, with visual acuities of 0.1 or worse and discrete central scotomata in all, that the only clinical or laboratory evidence for differentiation we could find among them was the presence of mtDNA mutations. This raised two questions: Were the mtDNA mutation-positive and -negative optic neuropathies etiologically similar or overlapped? Did the simple classification of patients with bilateral optic neuropathy, based on the known mtDNA genotypes, have clinical significance and validity? One of the reasons we could not address these issues was the lack of understanding of the precise locus in the visual sensory pathway involved in LHON. In this regard, some physicians think primarily retinal ganglion cells may be involved, whereas others agree that LHON may be primarily a microvascular disorder. A recent report indicated that the direct pupillary light reaction is well preserved and that X and Y retinal ganglion cells may be impaired selectively in patients with LHON.

Photic blink reflex (PBR) is blinking evoked by sudden illumination, which is known to consist of early and late responses. The early response of PBR is constantly demonstrated in normal subjects and is delayed or extinguished in patients with various types of optic nerve disorders. It is suggested that the afferent fibers of the early response of PBR enter the brainstem and terminate presumably in the pretectum.
in humans,$^{20,21}$ as some of the afferent fibers of the light reaction do. In this study, we examine whether the early response of PBR also is spared in patients with LHON and compare the results with those in bilateral optic neuropathy of other etiologies. The purposes of this study are to understand further the PBR pathway, to elucidate the characteristic impairment of visual function in patients with LHON, and to assess the validity of the molecular biology-based classification of patients with bilateral optic atrophy.

**MATERIALS AND METHODS**

**Subjects**

We recruited 26 patients diagnosed with bilateral optic neuropathy from the outpatient clinic of Kobe University Hospital. The criteria for enrollment in the study were decline of visual acuity to 0.1 or below, presence of central scotomata on Goldmann kinetic perimetry, age at testing for blink reflex from 10 to 59 years (see below), absence of intraocular abnormalities other than optic atrophy, and a follow-up period of at least 6 months after the first eye involvement. Presence or absence of family history was not included in the enrollment criteria. Computed tomography and magnetic resonance imaging of the brain and orbit were performed on all patients. Cerebrospinal fluid examination, including assessment of the oligoclonal immunoglobulin G band, was performed on all patients with a fresh illness. These patients included one with multiple sclerosis who was diagnosed according to the guidelines of Poser et al$^{22}$ after a full neurologic examination, two patients with autosomal dominantly inherited optic neuropathy determined by definite family history, and one patient with dysthyroid optic neuropathy.

In addition, 20 age-matched healthy volunteers were tested for mtDNA mutations and blink reflexes.

The research followed the tenets of the Declaration of Helsinki and was approved by the human experimentation committee of Kobe University Hospital. Informed consent was obtained from all participants.

**Classification of Subjects Based on the mtDNA Mutations**

Whether the 26 patients and 20 healthy volunteers had three primary mutations at nucleotide position 3460, 11778, or 14484 of mtDNA$^{2-6}$ was examined. These are known to be specific for LHON and have pathologic significance. The detailed method of mtDNA analyses using polymerase chain reaction technique was described previously.$^{23-25}$

After the 26 patients were divided into 11 mutation-positive and 15 mutation-negative subgroups, descriptive data—including age at onset, sex ratio, visual acuity, width of central scotoma, and latency of blink reflex—were compared between the two patient groups. Landolt visual acuity testing was carried out with the viewing distance set at 5 meters, and the outcome was expressed as a decimal unit. For testing the visual fields, Goldmann kinetic perimetry was used because many patients with optic atrophy producing large central scotoma cannot identify the central fixation target readily and must be encouraged to sustain central fixation during the test. Thus, computed static perimetry is not suitable for evaluating the visual field defects in such patients. Central scotoma was defined as a big scotoma if it extended beyond 10° of fixation with 1—4 stimulus and as a small one if it did not.

**Assessment of Blink Reflex Response**

In this study, we evaluated blink reflex responses evoked by an electrical stimulation of the supraorbital nerve (evoked blink reflex [EBR]), as well as those evoked by flash light (PBR) because although the afferent pathways of the two reflexes are different (the former, the first branch of the trigeminal nerve; the latter, the optic nerve), the efferent pathway is common (the facial nerve). A comparative evaluation of these responses, therefore, has been known to yield significant information for the diagnosis and identification of a specific locus of neurologic impairment.$^{13-17}$ A discrepancy between a normal EBR response and an abnormal PBR response in the same person indicates specific impairment of the optic nerve, whereas a normal PBR response but an abnormal EBR response (which has not yet been reported) would implicate selective involvement of the trigeminal nerve. If both blink reflexes are impaired simultaneously, either the common efferent facial nerve alone or multiple regions of the central nervous system are thought to be involved.

The responses were recorded by electromyography of the orbicularis oculi muscles in the lower eyelid using Neuropack 4 MEM-4104 (Nihon Koden, Tokyo, Japan) as described previously.$^{17-19}$ Two round surface electrodes were placed over the inferior—lateral quadrant of the muscle, and the position was adjusted to obtain the maximum voltages. A reference electrode was located on the right earlobe.

For recording the EBR response, isolated electrical stimuli of a square pulse were delivered to the supraorbital nerve through a bipolar electrode located on the skin over the supraorbital foramen.$^{15,14,17,18,26}$ The stimuli had a duration of 0.2 msec and were of such intensity (10 to 20 mA) that reflex responses were just maximal and nearly stable with repeated trials at random intervals (least interval = 1 minute). This reflex has been known to consist of ipsilateral early response (R1) and bilateral late responses (R2).$^{13,14,20,27}$ Whether the terminations of the R1 and R2 afferent
trigeminal pathways are the same (superior sensory nucleus) or different (superior and inferior sensory nuclei, respectively) is a controversial matter. The latencies of the R1 and R2 components ipsilateral to the stimulated sides were measured.

For recording the PBR response, subjects were tested in the supine position and were instructed to look down approximately 15° to eliminate background electromyography activity in the muscle. The lamp was fixed at a distance of 20 cm from the eye, and the lamp parabola was fixed at right angles to the eyeball axis. All tests were carried out in a dark room. After a 15-minute adaptation to darkness, light stimuli with an intensity of 20 J were delivered at random intervals (least interval = 1 minute) to the right and left eyes independently, with the other eye covered by an opaque mask. The PBR response also consists of early- and late-phase components. It has been well known, however, that the onset of the late PBR response cannot always be recognized distinctly, whereas the early response constantly appears and its latency is stable in healthy young and middle-aged adults. Thus, the latency of the early response was determined to represent the latency of PBR in this study, as it was in previous studies. On the other hand, the latency of PBR in children, especially those younger than 7 years of age, and in elder subjects could be delayed. The testing age for the blink reflex, therefore, was restricted to those 10 to 59 years of age. The light flash stimulus of 20 J was adopted for the current study because we previously determined that this intensity was sufficient enough to evoke the least variable PBR response under the condition tested. Latency to the earliest electromyography discharge of the orbicularis oculi muscles on the same side as the stimulated sides was measured.

At least 10 responses for each subject were collected, and the shortest latency was determined to represent the latency of the blink reflex response for the subject. Latencies were judged abnormal if they exceeded the mean value for controls over 3 × SD.

Statistics
Mann–Whitney testing was conducted for comparison of age at onset, age at testing for the blink reflex, or duration from onset to testing between the two patient groups. Age at testing for the blink reflex in the control subjects was compared with those in each patient group. Fisher’s exact probability test was used for comparison of the ratio of big versus small scotomata or the ratio of normal versus abnormal latencies of the blink reflex responses between the two patient groups.

RESULTS
No mutations were found in the 20 healthy volunteers. Descriptive data and latencies of the blink reflex responses in the mtDNA mutation-positive and -negative groups are shown in Tables 1 and 2, respectively.

In the former group, patients 1 to 3, who had affected maternal relatives, had typical disc findings at the initial examination. Patients 4 and 5 had typical disc findings but no family history. Patients 6, 7, and 9, with their histories of substantial tobacco and alcohol use, showed reduced concentrations of several B group vitamins, and, thus, previously had been diagnosed with tobacco–alcohol amblyopia or deficiency optic neuropathy. The remaining patients had no family history and no objective signs of LHON, nor any other intraorbital, intracranial, or systemic disorders, and they had been diagnosed with retrobulbar optic neuritis before the detection of the mutations (Table 1).

In the latter group, except for patients 23 (clinically probable multiple sclerosis), 24 and 25 (autosomal dominantly inherited optic neuropathy), and 26 (compressive dysthyroid optic neuropathy), no apparent intraocular, intraorbital, intracranial, or systemic pathology was detected throughout the follow-up period. Optic atrophy had already developed in patients 12 to 17 at the initial examination. Patients 16 and 17 were suspected to have autosomal dominantly inherited optic neuropathy because of the early age of onset, wedge-shaped optic atrophy, and tritan-type acquired dyschromatopsia, but the diagnosis was not confirmed because of the lack of a definite family history. Patients 18 to 22 exhibited normal disc findings at first, followed by the development of optic atrophy, and they were diagnosed with retrobulbar optic neuritis (Table 2).

Neither age at onset of optic neuropathy (P = 0.50) nor at testing for the blink reflex (P = 0.46) was significantly different between the two patient groups. The age at testing in the control subjects ranged from 10 to 56 years, with an average of 33.0 ± 12.8 years, which did not differ from those of the mutation-positive (P = 0.49) or mutation-negative group (P = 0.45). The duration from age at onset to age at testing ranged from 1 to 8 years in the mutation-positive group and 1 to 42 years in the mutation-negative group; this was not statistically different (P = 0.44).

When a big scotoma was defined as larger than 10°, and a small scotoma was defined as equal to or smaller than 10° with a 1 – 4 stimulus on Goldmann perimetry, the ratio of the big versus small scotomata in the mutation-positive group was significantly higher (P = 0.02) in the mutation-positive group (9 versus 2) than in the mutation-negative group (5 versus 10).

All patients with the mtDNA mutations exhibited diffuse optic atrophy. Patients 16 and 17 showed temporal disc pallor, whereas the others in the mutation-negative group showed diffuse optic atrophy.

Average latency of the PBR early responses in the
Photic Blink Reflex in Leber’s Disease

TABLE 1. Descriptive Findings and Blink Reflex in Patients With Mitochondrial DNA Mutations

<table>
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<tr>
<th>Case Number</th>
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<th>Onset Age (years)</th>
<th>Test Age (years)</th>
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<th>VFD</th>
<th>PBR</th>
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Test age = analyses of both mitochondrial DNA and blink reflex were concurrently performed; RE = right eye; LE = left eye; VA = corrected visual acuity; CF = counting fingers; HM = hand motion; VFD = size of central scotoma measured on Goldmann perimetry; PBR = latencies of the early response of photic blink reflex (msec); NR = nonrecordable; EBR = latencies of electrically evoked blink reflex in RE (msec). Those in LE were omitted owing to absence of abnormal values.

20 control subjects was 50.3 ± 2.4 msec. Average latencies of the R1 and R2 EBR responses were 11.4 ± 0.8 msec and 57.7 ± 3.1 msec, respectively. These values were in good agreement with the corresponding values previously reported by us17-19 and by others,13-16 indicating that the latencies of both blink reflex responses in normal subjects during these ages were fairly stable. Photic blink reflex latency was judged normal if it was above 57.5 msec, whereas R1 and R2 components of EBR were regarded as abnormal if they were above 13.8 msec and 47.0 msec, respectively.

All but one patient with the mtDNA mutations exhibited normal latencies of the PBR responses, whereas 12 of 15 patients with no mutations showed prolonged latencies (Table 1, 2; Figs. 1, 2, 3). The ratio of normal versus abnormal PBR responses was statistically higher (P = 0.0005) in the mtDNA mutation-positive group than in the mutation-negative group. A patient with the mtDNA 11778 mutation, whose PBR response was extinguished (patient 9), showed delayed EBR responses as well (Table 1). Except for this patient, no abnormal EBR responses were observed.

TABLE 2. Descriptive Findings and Blink Reflex in Patients Without Mitochondrial DNA Mutations

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Sex</th>
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<th>Test Age (years)</th>
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<th>VFD</th>
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OA = optic atrophy, etiology of which was not determined; ON = idiopathic optic neuritis; MS = multiple sclerosis; ADON = autosomal dominant optic neuropathy; DO = dysthyroid compressive optic neuropathy; NR = nonrecordable; CF = counting fingers; RE = right eye; LE = left eye; VA = corrected visual acuity; VFD = size of central scotoma measured on Goldmann perimetry; PBR = latencies of the early response of photic blink reflex (msec); EBR = latencies of electrically evoked blink reflex in RE (msec).
FIGURE 1. Comparison of latencies of the early response of photic blink reflex in the right eyes of patients with optic neuropathy with and without mitochondrial (mt) DNA mutations, either at nucleotide position 3460 or 11778. Open and closed circles indicate patients with and without the mutations, respectively. Bar = upper limit of normal range. NR = nonrecordable. Similar results were obtained in the left eyes (see Tables 1, 2).

FIGURE 2. Development of central scotoma and conserved response of photic blink reflex in patient 4. Relative central scotoma at initial examination (upper left) develops into large absolute cecocentral scotoma 6 years later (upper right). Normal latency of the early response (arrowheads) at initial examination (lower left, 51.2 msec) is unchanged after 6 years (lower right, 49.5 msec).

response in patient 9 was thought to be attributable, at least in part, to the impairment of the common efferent pathway of both blink reflex arcs, and/or to the rare coincidental impairments of both optic and trigeminal nerve afferent fibers. Patient 4 had bilateral myelinated optic nerve fibers, which decreased in number during the 6-year follow-up period. Repeat examinations of the PBR response always demonstrated normal latencies (Fig. 2).

The similar poor visual acuities of the two patient groups, in accordance with the enrollment criteria, and the semiquantitative nature of the blink reflex responses precluded us from estimating the statistical correlation between visual acuity and blink reflex response.

DISCUSSION

Previously, we reported that various causes of optic neuropathy—such as trauma, ischemia, mechanical compression by pituitary tumor—and of demyelination—such as multiple sclerosis—can cause prolongation of the early response of photic blink reflex (PBR). The current study has demonstrated that the response was impaired not only in patients with idiopathic optic neuritis and multiple sclerosis but also in those with autosomal dominantly inherited optic neuropathy or dysthyroid optic neuropathy in the mtDNA mutation-negative group. In contrast, the
FIGURE 3. A representative patient without the mtDNA mutations (patient 24; Table 2). (upper) Kinetic perimetry in the right eye, showing small scotoma. (middle) Electrically evoked blink reflex response. Upper wave shows the response in the stimulated right eye. Normal latencies of R1 (black arrowhead, 11.5 msec) and R2 (white arrowhead, 36.7 msec), respectively, are shown. Lower wave shows normal latency of R2 (white arrowhead, 40.1 msec) in the left eye. (lower) Photic blink reflex response in the right eye is shown. Delayed latency of the early response (arrowhead, 62.8 msec) is noted, indicating selective impairment of the optic nerve.

early response of PBR was found to be well preserved in the current patients with LHON with the tested mtDNA mutations. Distributions of onset ages and visual acuities and optic disc findings were similar between the two patient groups. The ratio of big to small central scotomata was higher in the mutation-positive group than in the mutation-negative group. On the other hand, the ratio of normal to abnormal PBR responses in the mutation-positive group was significantly higher than that in the mutation-negative group. Interestingly, a patient with LHON (patient 4) did not show any prolongation of the PBR latency during the 6-year follow-up period, despite a decrease in the number of myelinated nerve fibers (Fig. 2). Together with the observation that the various nonde-myelinating diseases have a potential for extinguishing the PBR response, preservation of normal latency of the PBR early response cannot be ascribed to absence of demyelination in LHON. Despite similar clinical findings, the primarily pathologic focus in the visual sensory pathway in LHON is probably distinct from that in bilateral optic neuropathy of other causes. In this regard, Wakakura and Yokoe reported that the direct light reaction is well preserved in patients with LHON. They speculated that, because W cells are thought to function as a luminance detector and to provide input to the pupillary light reaction, the tonic on-center W retinal ganglion cells might be selectively spared in them. Other physicians also noted the brisk light reaction in patients with LHON.

Although the precise pathway of PBR is still unknown, its early response has been indicated to take the subcortical pathway. The fair responses of blinking to sudden light flashes in comatose patients, whose cerebral cortices were fatally damaged, have suggested that the reflex arc is mediated by the brainstem in humans. Tavy et al. further reported that the afferent fibers of the blink reflex to light could terminate in the pretectum, which is known to be one of the important centers for the light reaction. In primates, a direct or indirect projection from the olivary pretectal nucleus to the facial nucleus has been demonstrated, and a retino-pretecto-facial pathway seems to be the main reflex arc for the early response of PBR. In cats, the afferent pathway of the early response of PBR is suggested to be composed of uncrossed retinal fibers, and the tonic W cells in the temporal retina project uncrossed fibers to the ipsilateral side of the midbrain. Therefore, the preservation of the early response of PBR, in concert with the preserved direct light reaction in patients with LHON, indicates that retinal ganglion cells, functionally analogous to the cat tonic on-center W cells, may project some common afferent fibers of these two neuronal systems and may be preferentially spared in LHON. In addition, the above lines of evidence seem to support the validity of classification of patients with bilateral optic neuropathy simply according to the presence of the known primary mtDNA mutations.

On the other hand, 3 of the 15 patients with optic neuropathy without the mtDNA mutations also had the normal PBR latencies. Possibly, these three pa-
tients were affected with LHON but had a yet unidentified mtDNA mutation. Another possible explanation is that they were affected with bilateral optic neuropathy other than LHON, which also preserved the normal PBR response. For example, tobacco–alcohol amblyopia or deficiency optic neuropathy has been suggested to involve P cells specifically, almost identical to X cells in cats, and parvocellular layers of the lateral geniculate nucleus. In other words, W cell-like neurons could be intact; thus, PBR would be expected to be preserved. Interestingly, clinical findings of tobacco–alcohol amblyopia or deficiency optic neuropathy have been known to simulate those of LHON, including male predilection, bilateral optic disc swelling, and peripapillary microangiopathy without the fluorescein dye leakage in the acute stage and the subsequent development of central scotoma and optic atrophy. Because of phenotypic similarities among these diseases, LHON—especially if it is of nonfamilial origin—is sometimes misdiagnosed as tobacco–alcohol amblyopia or deficiency optic neuropathy until the mtDNA analysis is complete. This happened with patients 6 and 7 in the current study. The pathophysiology, pathologic loci, or both on the visual sensory pathway of these disorders may be identical or very similar. Recently, Rizzo suggested that adenosine triphosphate deficiency may be a unifying etiology for LHON, tobacco–alcohol amblyopia, and/or deficiency optic neuropathy, and that the variations in the supply and demand of energy to specific retinal ganglion cells may determine the degree of the development of central scotoma and optic atrophy. We also reported that several B-group vitamins are reduced in sera of patients with LHON and tobacco–alcohol amblyopia or deficiency optic neuropathy. Further understanding of the pathophysiology of these disorders is needed before any conclusions can be drawn.

In summary, the early response of PBR is well preserved in patients with LHON. The dissociation of big central scotoma and normal PBR response in patients with bilateral optic neuropathy is highly supportive of the diagnosis of LHON. Because the light reaction also is preserved in patients with LHON, we presume that the tonic on-center W retinal ganglion cells may project, at least in part, afferent fibers of the early PBR response and may be preferentially spared in LHON. It is our opinion that the mtDNA analysis–based classification of patients with bilateral optic neuropathy and its application to clinical practice are justifiable.

**Key Words**

Leber’s hereditary optic neuropathy, light reaction, mitochondrial DNA mutation, photic blink reflex, retinal ganglion cells

**References**

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