Clinical Features of Leber's Hereditary Optic Neuropathy with the 11778 Mitochondrial DNA Mutation in Taiwanese Patients

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Background: To characterize the clinical features of Leber's hereditary optic neuropathy (LHON) in Taiwanese patients with the 11778 mutation of mitochondrial DNA (mtDNA).

Methods: A retrospective review of the clinical manifestation was undertaken in 13 LHON patients with the 11778 mtDNA mutation from 1994 to 2001 in Chang Gung Memorial Hospital.

Results: The male-to-female ratio among patients was 12:1 (92% male). The age at onset of visual loss for the first eye ranged from 7 to 30 years old, with a mean of 19.4 years. The time interval between when the second eye was affected ranged from simultaneous onset to 7 months (mean, 2.2 months). The final visual acuity was 0.1 or worse in 24 eyes (92.3%). A suspect fundus was present in 14 of 26 eyes (54%). Patients with later onset of visual loss (<20 years) tended to have better final visual acuities. Abnormal visual evoked potentials (VEPs) were recorded after acute onset of visual loss in all of our patients and even before onset of visual symptoms in 1 patient.

Conclusions: The clinical characteristics of our patients harboring the 11778 mitochondrial mutation are mostly similar to those previously reported from other countries. In addition to the common features of LHON, we also noted that there was a relationship between age of onset and visual prognosis. We also suggest that VEP is a good indicator for predicting visual loss.
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Key words: Leber's hereditary optic neuropathy, 11778 mutation, ethnic Taiwanese patients, visual recovery, age of onset.

Leber's hereditary optic neuropathy (LHON) is a maternally inherited mitochondrial disease that results in acute or subacute bilateral visual loss, particularly in young men. Several mtDNA mutations including those at nucleotide positions 11778, 3460, and 14484 have been proposed as primary mutations in the pathogenesis of LHON.[1] They are the most deleterious and are not found in normal controls. Among them, the 11778 mutation is most important and accounts for 50% to 70% of LHON patients in several studies.[2-5] Visual prognoses in LHON patients are usually poor, especially in patients with the 11778 mtDNA mutation. In addition, a recent Chinese study demonstrated that a homoplasmic 11778 mutation was exclusively present in 92% of LHON patients.[6] However, the clinical manifesta-

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tions and outcomes have not yet been described in detail in Taiwanese patients with the 11778 mutation. In this study, we attempted to understand the clinical features and visual outcomes in Taiwanese patients with LHON harboring the 11778 mutation.

METHODS

We enrolled 13 patients with LHON referred to the Neuro-ophthalmology Department of Chang Gung Memorial Hospital from 1994 to 2001. All of them had the 11778 mtDNA mutation as confirmed by a previously described DNA analysis of blood samples.[6]

This study was based on a review of the medical records, fundus photographs, and neuro-ophthalmologic examinations. The clinical information collected included the gender of the affected individual, the age at onset of visual loss, associated symptoms, the time interval between the second eye becoming affected, and the duration of progression of visual loss in each eye. Medical and family histories were obtained in as much detail as possible, with special attention to ophthalmic, neurologic, and cardiac diseases. Any known exposure to environmental toxins, tobacco, alcohol, and drugs was also recorded.

Ophthalmic examinations included final visual acuity, color vision, visual field tests (Humphrey 30-2 program), and ophthalmoscopic findings recorded by fundus photographs. The results of other ancillary tests including visual evoked responses, brain computed tomography, brain magnetic resonance imaging, and electrocardiograms were included when available.

RESULTS

All 13 LHON patients were male except 1, producing a male-to-female ratio of 12:1 (92% male). The age at onset of visual loss for the first eye ranged from 7 to 30 years old, with a mean of 19.4 years. All patients without exception had involvement of both eyes. The time interval between the second eye becoming affected ranged from simultaneous onset to 7 months (mean, 2.2 months). The duration of progression of visual loss within each eye was reported in 14 eyes, and ranged from 2 weeks to 4 months. The mean time to stabilization was 1.6 months. Only 1 patient recalled having pain on movement during the acute visual loss period in his right eye.

The final visual acuity was variable, ranging from no light perception to 1.0. The visual acuity was 0.1 or worse in 24 eyes (92.3%) (Fig. 1). Seven eyes had improvement in visual acuity of variable degrees. In patient 3, the right eye improved from hand motion to 0.7, and the left eye improved from counting finger to 0.09 one year later. In patient 5, the right eye improved from hand motion to 0.01, and the left eye improved gradually from light perception only to counting fingers during the following 4 years. In patient 8, the right eye improved from light perception only to counting fingers after 16 months. In patient 10, the right eye improved from 0.02 to 1.0 sixteen months after onset, while the left eye improved from 0.02 to 0.1. Five patients had taken coenzyme Q10 for 4 months to 3 years with an increasing dose of from 90, 160, to 200 mg/day orally. Four of them had visual improvement as described above.

The visual fields evaluated in 12 patients showed central or cecocentral defects of variable sizes. The visual field defect enlarged during the course of the disease in all patients, except for 2 patients who had decreasing size of the cecocentral scotoma and who experienced improvement in their visual acuity (Table 1).

Ophthalmoscopic abnormalities other than optic

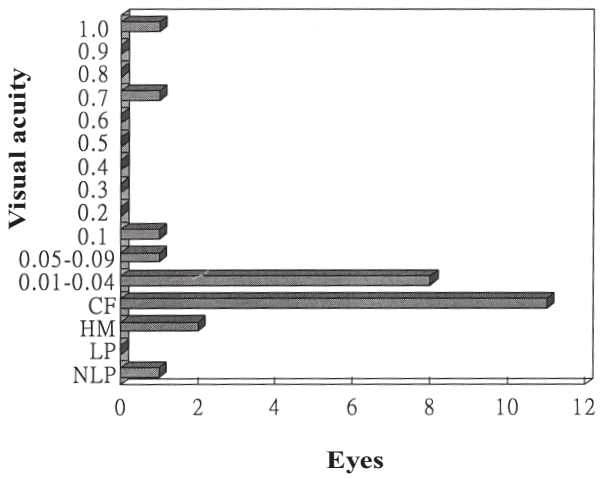

Fig. 1 Final visual acuity in 26 eyes.
Abbreviations: CF: counting fingers. HM: hand motion. LP: light perception only. NLP: no light perception.

atrophy were considered "suspect" in our study for the characteristic Leber's fundus appearance if photographs or ophthalmologists' descriptions disclosed disc edema, pseudoedema, hyperemia, telangiectatic microangiopathy, or vascular tortuosity. At least 1 of these findings was present in 14 of 26 eyes (54%) (Table 2). Forty-six percent of eyes were already showing optic atrophy by the time the patient first visited our clinic. After the acute stage, nerve fiber layer swelling decreased, the microangiopathy faded, vascular dilation and the tortuosity underwent vascular attenuation, and the optic disc became pallor (Fig. 2). Optic atrophy developed 3 months after onset in most of these patients, but it was as late as 6 months or even later in a few.

Four patients used tobacco, among whom, 1 also had alcohol abuse. One patient reported amphetamine abuse for 1 year before the onset of symptoms. Another patient had a head injury just before the first onset of visual loss, but lacked other neurological sequelae.

Electrocardiogram results were reported in 7 patients, none of which were abnormal. No neurological deficits other than optic nerve dysfunction

Table 1. Final Visual Field in 26 Eyes with LHON

Size of cecocentral scotoma					
	Normal or enlarged blind spot	<10°	10°-20°	>20°	Unknown
No.(%)	0(0)	2(7.7)	3(11.5)	19(73)	2(7.7)

Abbreviations: LHON: Leber's Herreditary Optic Neuropathy

Table 2. Fundal Abnormalities in 13 Patients with LHON

	Normal fundus	Retinal nerve fiber layer swilling	Peripapillary telangiectasia	Disc swelling or hyperemia	Retinal vascular tortuosity	Disc pallor
Duration visual loss (months)	Percentage of eyes					
<3 (n=14)	0	71	43	70	29	7
3-6 (n= 3)	0	67	0	0	33	33
>6 (n= 9)	0	0	0	0	0	100

Abbreviations: LHON: Leber's Hereditary Optic Neuropathy

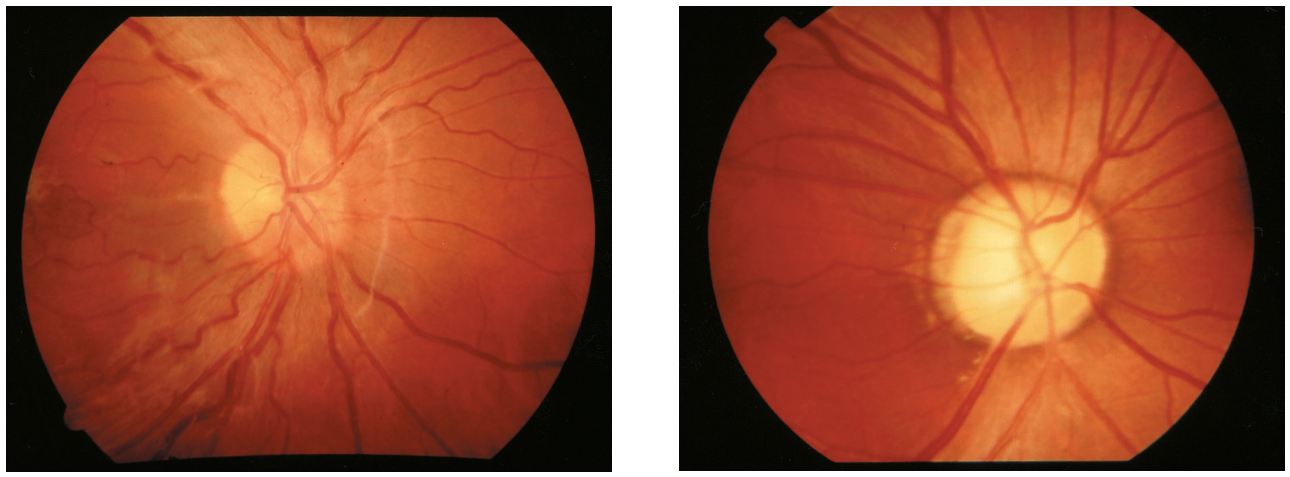

Fig. 2 Left: Suspect fundus at the acute stage including disc pseudoedema, hyperemia, nerve fiber layer swelling, telangiectatic microangiopathy, and vascular tortuosity. Right: Late stage. The disc has become paler on the temporal side, and nerve fiber layer loss has begun at the papillomacular bundle. Telangiectatic microangiopathy has disappeared, and the vascular tortuosity has decreased.

were noted in any of the 13 patients. Brain computed tomography or magnetic resonance images were reported as normal in 4 patients for whom they were performed. Visual evoked responses were absent in 12 of the 13 patients. In patient 12, we detected significant prolonged latencies and mildly diminished amplitudes of the pattern visual evoked response 2 weeks before the onset of visual symptoms. There were also fundus changes in the presymptomatic phase, including a hyperemic disc, increased visible microangiopathy, nerve fiber layer swelling, and retinal vessel dilatation.

DISCUSSION

To determine the clinical features of Taiwanese patients with LHON, we attempted to define the phenotype of the 11778 mtDNA mutation by compiling data from all such patients referred to us. We observed a predominance of affected males (92%), consistent with previous reports from Japan (92.1%)[7] and the US (82%).[8] The mean age at onset was 19.4 years with a range of between 7 and 30 years. A peak was observed in the second decade of life. The mean age in our study was lower than that reported by Hotta et al.[7] (23.4 years) and by Newman et al.[8] (27.6 years).

Two patients reported simultaneous onset of bilateral visual loss (15.4%), while 8 patients (61.5%) experienced an onset interval between affected eyes. The second eye usually became involved within 2 months, although the interval was as long as 7 months. The intervals were unclear in 3 patients. The mean duration of visual loss progression was 1.6 months, and stabilization in most patients occurred within 2 months. Therefore the clinical course was acute or subacute in the majority of our patients.

Our patients rarely had other symptoms at the time of acute visual loss. Although up to 18% of patients with the 11778 mutation had pain around the affected eye and 10% had pain on eye movement in a UK study,[3] only 1 of our patients reported pain on eye movement during the acute stage. Cardiac conduction abnormalities, specifically pre-excitation syndromes, have been associated with LHON in many pedigrees.[9] Over half of our patients had an electrocardiogram study, but none had cardiac arrhythmias. Numerous patients and maternally related family members have been diagnosed as having multiple sclerosis,[3,8] but such a correlation was not observed in our study or in a Japanese study.[10]

Generally, patients with the 11778 mutation have a poor visual outcome. In our study, 24 eyes (92.3%) had a final visual acuity of 0.1 or worse, which was slightly better than a previous American report (98.2%)[8] and worse than Japanese data (85.9%).[7] This may be due to racial differences. Visual recovery, defined as final visual acuity better than 0.4, was previously observed in only 4% of patients with the 11778 mutation;[4] whereas visual recovery occurred in 2 of our patients (15%). Both of these patients had received coenzyme Q10 treatment. In patient 3 who began to receive coenzyme Q10 treatment 6 months after onset, the right eye improved from hand motion to 0.5, and the left eye improved from counting finger to 0.2 within 3 months. In patient 10 who began to receive coenzyme Q10 treatment 3 months after onset, the right eye improved from 0.02 to 0.8, and the left eye improved from 0.02 to 0.1 within 11 months. The range of spontaneous recovery time was 12 to 71 months in previous studies.[3,7,8] The time of recovery for our patients was shorter compared to those of previous reports. Although the effect of coenzyme Q10 still needs to be determined, the results are nonetheless encouraging.[11] Further investigation is needed to clarify the therapeutic effect of coenzyme Q10 in LHON patients.

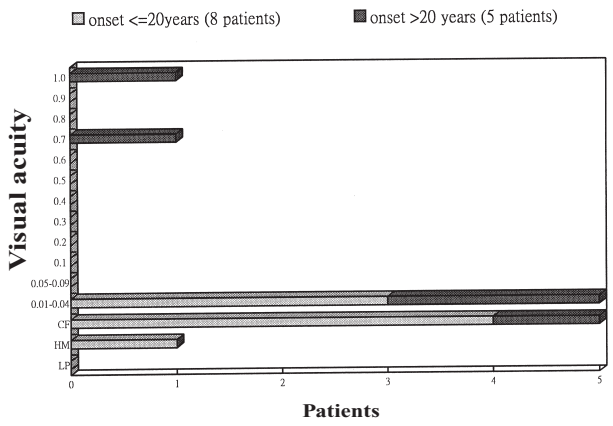

Fig. 3 Final visual acuities of the better eye in patients divided into 2 groups (onset at or before 20 years old, and onset after 20 years)

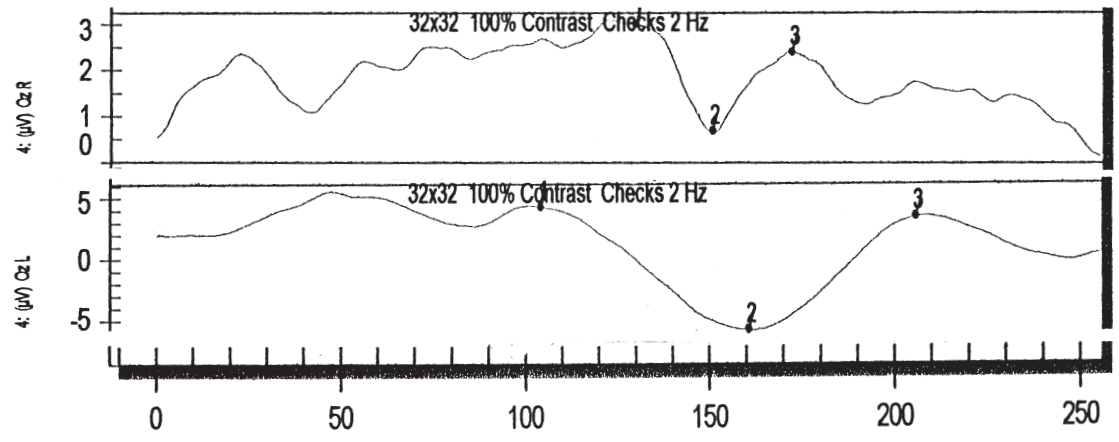

Fig. 4 Pattern visual evoked response stimulated by a 32×32 checkerboard in patient 12 during the onset interval. Top: Significantly prolonged latency and diminished amplitude of the pattern visual evoked response 4 months after onset in his right eye. Bottom: Significantly prolonged latency of pattern visual evoked response 2 weeks before the onset of visual symptoms in his left eye.

Riordan-Eva et al.[3] demonstrated that visual acuities are correlated with age of onset of visual loss in patients with the 14484 mtDNA mutation. Younger age of onset (≤20 years) was associated with a less-severe reduction in worst visual acuity and better final visual acuity. There was no such correlation in patients with the 11778 or 3460 mtDNA mutation in that study. We also found an association between age of onset and visual acuity in our study, but, on the contrary, patients with later onset of visual loss (≤20 years) tended to have better final visual acuity (Fig. 3).

In 1973, Smith et al. described classic ophthalmoscopic appearance of patients with LHON and acute visual loss: circumpapillary telangiectatic microangiopathy, swelling of the nerve fiber layer around the disc, and absence of staining on fluorescein angiography. Nikoskelainen et al.[12] noted typical peripapillary microangiopathy in all of their acutely symptomatic patients, some of their presymptomatic patients,[12] and even asymptomatic maternal relatives.[13] Similarly, all of our patients who were examined during the acute phase had at least 1 of the fundus changes described above. We even noted peripapillary microangiopathy progression during the presymptomatic phase of 1 patient. We also recorded subnormal VEP responses at the same time. Since microangiopathy is sometimes difficult to observe without fluorescein angiography, we suggest that VEP is a good indicator to predict onset of the disease. It can reveal subtle abnormalities in optic nerve function even before patients are aware of them (Fig. 4).

Four of our patients smoked cigarettes. One of them also consumed alcohol. Another patient reported using amphetamines before the onset of symptoms. Exposure to toxic substances, alcohol consumption, and cigarette smoking have all been proposed as potential precipitating factors because of their potential to cause respiratory stress. Results of recent investigations have supported this theory. Tsao et al.[14] demonstrated that smoking was significantly associated with disease penetrance in 1 LHON pedigree, with the degree and duration of smoking being correlated with increased risk of developing symptoms. One of our patients had visual loss in 1 eye within 1 month after experiencing head trauma. Subsequently, the other eye developed progressive visual loss 6 months later. Anecdotal reports also exist as to the presence of a traumatic insult preceding visual loss.[15] This suggests that trauma may play a role as an epigenetic risk factor.

In conclusion, the clinical characteristics of our patients harboring the 11778 mitochondrial mutation are mostly similar to those previously reported in other countries. What differs from other studies is

the relationship between the age of onset and visual prognosis. This has not been mentioned before. We also suggest that VEP is a good indicator for predicting the onset of visual loss.

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11778粒線體DNA突變的雷伯氏遺傳性視神經病變在台灣病人之臨床表徵

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背 景： 探索11778粒線體DNA突變的雷伯氏遺傳性視神經病變在台灣病人身上的臨床特徵。

方 法： 從1994年到2001年間，共有13位雷伯氏遺傳性視神經病變的病人，證實爲11778粒線體DNA突變，登錄於此回溯性研究。

結 果： 這13位病人當中，男女比例爲12比1 (92%爲男性)。視力下降發生年齡分布爲從7歲至30歲，平均爲19.4歲。兩眼間發病之間隔從同時發生到7個月不等，平均爲2.2個月。有24隻眼睛的最終視力低於或等於0.1 (92.3%)。有14隻眼睛的眼底出現異常的變化(54%)。20歲以後發病的病人有較好的最終視力。所有的病人其視覺誘發電位皆異常；甚至在一位病人身上，在其症狀發生前就已經出現異常。

結 論： 此研究中，我們的病人與其他地區的俱有11778粒線體DNA突變的雷伯氏遺傳性視神經病變之病人有許多共同的臨床表徵。不同的是，在我們的病人身上，我們發現發病年齡與視力的預後有密切的關聯。我們並且建議視覺誘發電位爲一預測發病之有利工具。

(長庚醫誌 2003;26:41-7)

關鍵字： 雷伯氏遺傳性視神經病變，11778突變，台灣病人，視力恢復，發病年齡。

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