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Original Article

Nationwide epidemiological survey of Leber hereditary optic neuropathy in Japan

Kaori Ueda [a], Yuki Morizane [b], Fumio Shiraga [b], Keigo Shikishima [c], Hitoshi Ishikawa [d], Masato Wakakura [e], Makoto Nakamura [a, *]

[a] Division of Ophthalmology, Department of Surgery, Kobe University Graduate School of Medicine, Kobe, Japan
[b] Department of Ophthalmology, Okayama University Graduate School of Medicine, Okayama, Japan
[c] Department of Ophthalmology, The Jikei University School of Medicine, Tokyo, Japan
[d] Department of Orthoptics and Visual Science, School of Allied Health Sciences, Kitasato University, Sagamihara, Kanagawa, Japan
[e] Inouye Eye Hospital, Tokyo, Japan

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ABSTRACT

Background: Leber hereditary optic neuropathy (LHON) is a maternally inherited optic neuropathy that leads to central loss of vision, predominantly in young males. Most LHON cases have one of three primary point mutations in mitochondrial DNA (mtDNA). The annual incidence and prevalence of LHON in Japan are not known. Thus, we estimated the annual incidence of molecularly confirmed LHON in Japan during 2014.

Methods: Sequential questionnaires were sent to 1397 facilities, which included all of the university hospitals in Japan, and they were certified by either the Japanese Ophthalmological Society or the Japanese Neuro-Ophthalmological Society. We calculated the incidence number (I_r) as the number of patients who developed LHON in 2014 and its 95% confidence interval.

Results: We received 861 responses to the first questionnaire, where 49 facilities reported 72 cases (67 were male and 5 were female) of newly developed LHON during 2014. I_r was calculated as 117, and the 95% confidence interval ranged from 81 to 153. For the second questionnaire, responses were received from 30 facilities, where the median age at onset was 38 years for males and 30 years for females, and 86.5% of cases possessed the mtDNA ND4/G11778A mutation.

Conclusion: Approximately 120 cases of newly developed LHON were reported during 2014 in Japan, and 93.2% were males.

Introduction

Leber hereditary optic neuropathy (LHON) is a maternally inherited optic neuropathy characterized by acute or subacute, bilateral, painless central vision loss and eventual optic atrophy.[1–3] LHON was the first disease to be identified as a mitochondrial DNA (mtDNA) mutation-associated human disorder. Over 95% of patients with LHON have one of the three primary point mutations in their mtDNA genes. These point mutations affect genes that encode subunits of the oxidative phosphorylation enzyme complex (ND), ND1/G3460A, ND4/G11778A, and ND6/T14484C, which are referred to as the "primary" mutations.[1–4] These mtDNA mutations are thought to disrupt electron transfer and increase oxidative stress, leading to apoptotic death of the retinal ganglion cells, the axons of which form the optic nerves.[1–6]

Patients with LHON experience a marked reduction in visual acuity and deep central scotoma. Unlike patients with optic neuritis, those with LHON exhibit no abnormal findings on performing gadolinium-enhanced magnetic resonance imaging of the optic nerve during the acute phase of the disease, and they do not respond to steroid therapy.[1,7]

LHON predominantly affects males, in whom onset occurs at adolescence or later, and it usually affects one eye initially and the other subsequently, with a mean interval of 2 months between onset in both eyes.[1,7] Up to 50% of males and 25% of females who are

* Corresponding author. Division of Ophthalmology, Department of Surgery, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan.
E-mail address: manakamu@med.kobe-u.ac.jp (M. Nakamura).
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related through matrilineal descent to individuals with a LHON pedigree manifest symptoms. Most patients with LHON suffer from permanent vision loss, but a small fraction of patients experience spontaneous recovery of vision, even long after the onset of the disease.[1–3,7] Unlike other mitochondrial diseases, most patients with LHON do not manifest neurological symptoms other than bilateral optic neuropathy, although subclinical cardiac or skeletal muscle abnormalities have been reported.[1,7] Mutations in mtDNA alone cannot entirely account for the unique features of LHON. Therefore, additional genetic, epigenetic, or environmental factors probably influence LHON expression among pedigrees that harbor the mtDNA mutations.[8]

As found with other types of mitochondrial diseases, the prevalence and incidence of LHON have been difficult to determine because this disease is rare and burdensome to diagnose. Previous epidemiological studies have reported that LHON cases where the patients have one of the primary mtDNA mutations have a minimum point prevalence of 1 in 31,000 in the Northern United Kingdom, 1 in 39,000 in the Netherlands, 1 in 48,000 in Finland, 1 in 54,000 in Denmark, and 1 in 113,300 in Australia.[4,9–11] However, a recent study reported a minimum point prevalence of 1 in 526,000 in the Serbian population, demonstrating a possible difference in the prevalence of LHON among diverse ethnicities.[12]

Two previous epidemiological studies of LHON have been conducted in Japan using relatively large sample sizes. In 1973, Imachi et al[13] evaluated the inheritance patterns and clinical features of 38 LHON pedigrees and 63 suspected pedigrees based on a family register and detailed clinical examinations. However, their study was conducted at a single institute and during the pre-molecular biology era. Therefore, the diagnosis of LHON may have been inaccurate, and the study may have included cases of optic neuropathy that were unrelated to LHON. Approximately 20 years later, Hotta et al[14] conducted a survey by sending a questionnaire to 86 university hospitals and reported the clinical features of 89 patients (79 pedigrees) with the ND4/G11778A mutation from 64 institutes that responded to the questionnaire. The questionnaire was not sent to facilities other than universities, and the subjects comprised both newly developed and long-standing cases. The inclusion of the long-standing cases was thought to have led to a biased underestimate because of the dropout of a non-negligible number of patients during follow-up. In addition, patients with the other two primary mtDNA mutations were excluded from the study. Thus, these findings could not estimate the incidence or prevalence of LHON because of their incomplete study designs and selection bias. However, they provided the important insight that female penetrance might have decreased through generations, such that the proportion of males in Japanese LHON cases was reported to be 68% in 1973 but 92% in 1995.[13,14] Further epidemiological studies could help to understand the factors that trigger and regulate the symptoms of LHON in mtDNA-mutated individuals, which may facilitate the development of an effective treatment in the future.

Thus, in the current study, we estimated the annual incidence of LHON during 2014 based on a nationwide questionnaire survey as a first step toward assessing the number of patients with LHON in Japan.

Materials and methods

Enrollment and exclusion criteria for subjects

In this study, we used sequential questionnaires to estimate the incidence number (I_r) as the number of patients with newly developed LHON during 2014. This study design was approved by the Ethics Committee of Kobe University Graduate School of Medicine (article No. 1711).

The diagnosis of LHON was based on the designated criteria for LHON established by the Research Committee on the Epidemiology of Intractable Diseases of Retinochoroidal and Optic Nerve Atrophy in conjunction with the Japanese Neuro-ophthalmological Society, and authorized by the Ministry of Health, Labour and Welfare, as listed in Table 1.[7] According to the designated criteria, the diagnosis of LHON was classified into the following three categories: *definite*, *probable*, and *possible* LHON cases. In this study, we enrolled patients with LHON who had one of the three primary mtDNA mutations. Therefore, cases of *definite* and *probable* LHON were included in our study, whereas those of *possible* LHON were not considered eligible. In addition, to be eligible for the current survey, a patient had to have a recent onset of LHON and been diagnosed in the year 2014.

Questionnaire methods

The first questionnaire simply determined the total number and sexes of new patients with LHON during 2014 who satisfied the designated criteria for *definite* or *probable* LHON.[7] In January 2015, this questionnaire was mailed directly to the heads of 1397 facilities, which comprised 1015 facilities certified by the Japanese Ophthalmological Society, including all university hospitals and 382 facilities with one or more affiliated member of the Japanese Neuro-ophthalmological Society. We asked the heads of these facilities to respond to the questionnaire by the end of March 2015.

After compiling the results of the first questionnaire, we mailed a second questionnaire to the heads of the facilities that reported new patients with LHON in the first questionnaire. The second questionnaire requested detailed clinical and genetic information for individual patients, including information regarding the age of onset and the positions of mtDNA mutations.

Incidence rate estimation

The number of patients with newly developed LHON during 2014 was estimated using the following formula, in accordance with previous studies[15–17]:

$$I_r = \frac{\sum \mathrm{i} \cdot N_i}{N/n},$$

where I_r denotes the estimated true number of patients (as units of patients with newly developed LHON), i actual number of patients ($i = 0, 1, 2\ldots$), Ni number of responding facilities with i patients, N total number of responding facilities, and n the total number of surveyed facilities.

In previous similar epidemiological surveys of intractable diseases,[15–17] the facilities were often selected randomly using stratified sampling from all of the facilities visited by a patient with a disease of interest. Thus, the number of surveyed facilities is usually much smaller than the total number of facilities when the corresponding facilities are classified into a stratum of general hospitals or clinics with a smaller number of hospitalized beds. In this situation, n is assumed to be much bigger than the number of facilities surveyed. However, we assumed that incident LHON cases were referred relatively immediately to facilities with affiliated specialists who had knowledge of LHON for the following reasons. First, individuals with a recent onset of LHON notice a rapid and profound decline in their central vision in both eyes, but they rarely exhibit extraocular symptoms. Second, given the necessity for molecular diagnosis and the unresponsiveness to steroid therapy, these patients are highly likely to be referred to tertiary or special institutes with affiliated neuro-ophthalmological specialists. The facilities to which we sent the first questionnaire covered most of these specialists. Thus, all of the facilities were considered to be

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