CLINICAL INVESTIGATION

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# A pedigree of Leber's hereditary optic neuropathy with visual loss in childhood, primarily in girls

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**Abstract** ● Background: Leber's hereditary optic neuropathy (LHON) mostly affects young males. In patients carrying one of the primary mutations the risk to develop LHON is 50% for males and 10% for females. We report a family with predominantly young girls affected. ● Methods: In a family with 14 known maternal relatives (11 females, 3 males) 9 patients in 4 generations developed LHON. Eight of the 9 patients were females. Three affected females could be examined and followed. ● Results: The only affected male showed the typical course of LHON with acute visual loss in both eyes (20/400–20/800) within 6 weeks at 20 years of age. Eight of 9 females developed signs of LHON. In these females acute visual loss occurred at about 10 years of age. Final visual acuity was about 20/200. Central or paracentral scotomata, color vision defects and delayed P100 latencies in the VEP were seen. Ophthalmoscopy showed hyperemic discs in the acute stage and optic atrophy in later stages. Molecular genetic analysis revealed the presence of the mtDNA ND4/np11778 mutation in this family. Specific clinical or additional molecular genetic risk factors could not be detected. ● Conclusion: Families with LHON may show considerable variations of the clinical course and the gender- or age-specific risk. We present a family with a high disease penetrance of 64% and a 2 times higher risk for young females than for males. Furthermore, early visual loss in this family is permanent.

## Introduction

Leber's hereditary optic neuropathy (LHON) is a maternally inherited disorder. Usually affecting young males, the disease presents with sudden onset of bilateral simultaneous or sequential visual loss in early adulthood [7, 14]. Centro-cecal scotomata, abnormal color vision and pathological VEPs are usually present. In the early stages, optic disc edema and peripapillary teleangiectasia may be found. Later, the optic disc may become pale and atrophic. In the majority of cases, loss of central vision is permanent, although cases of improvement of visual acuity have been reported in some patients [1, 8, 9, 17, 26].

Onset of LHON can vary considerably. Cases with onset as early as 6 years as well as over 60 years have been reported. The mean age of onset for patients carrying the nucleotide position (np) 11778 mutation is 27 years for males and 26 years for females [17]. Recovery of vision is more likely with an early onset of visual loss before the median age of about 27 years and in patients carrying the np14484 mutation [22, 23].

Point mutations in the mitochondrial DNA (mtDNA) at np11778, np3460, np14484 and np14498 are found exclusively in LHON pedigrees and are therefore designated as primary mutations. About 50–70% of all cases of LHON carry the np11778 mutation [27]. A ratio of 4.2 affected males to 1 female has been reported in a large multicentric study [19]. There is no explanation for the different risk for males and females. It has been suggested that the manifestation of LHON requires a second

**Fig. 1** Pedigree drawing of the LHON family reported in this paper. *Squares* represent males and *circles* females. *Solid symbols* represent subjects with visual loss
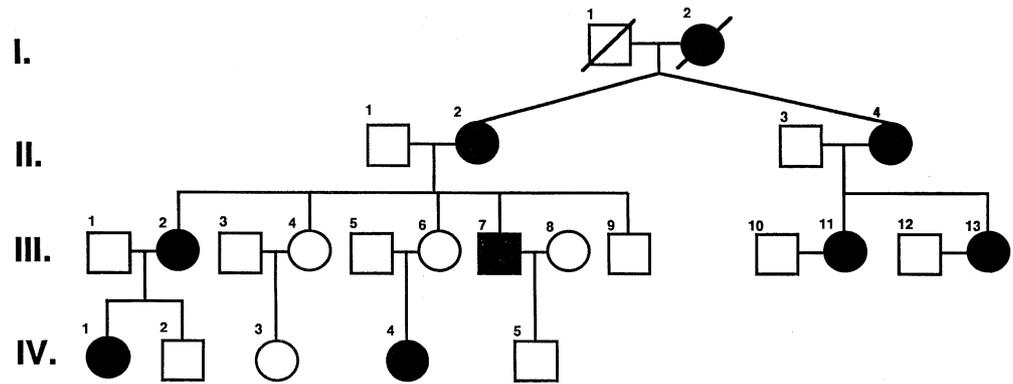


factor in addition to the primary mutation. An X-linked factor has been proposed, as well as specific male to female liability. However, these findings remain controversial [3–5, 10, 13, 16, 27]. The majority of carriers of the mutation remain asymptomatic, since only 30–50% of the males and 5–15% of the females develop symptoms of the disease.

In this study we report a family in which young females are predominantly affected in early childhood with no tendency of visual recovery despite visual loss occurring at an early age. We were able to follow three patients of this family. MtDNA mutation analysis was performed in six family members using DNA sequencing and PCR/RFLP analysis.

## Methods

A family affected with LHON in four generations with a total of 14 individuals was evaluated (Fig. 1). This family has not been examined and reported before.

Follow-up of the patients started in January 1993. Patients were asked about their visual loss, and previous records were obtained. A basic ophthalmological examination was performed as well as a desaturated Panel D15 color test, Goldmann perimetry and recording of visual pattern evoked potentials (VEP) according to published standards [8]. We were able to follow three patients over a period of 3 years. Blood samples were taken from three affected (III/7; III/2; IV/1) and three unaffected maternal family members (III/4; III/6; III/9) for molecular genetic analysis. Total DNA was extracted according to standard procedures. For mutation analysis, segments of the mtDNA were amplified by PCR and used for RFLP analysis. Mutation sites at np11778, np13708 and np4216 were analyzed in available subjects. Furthermore, np3460, np4160, np4917, np9804, np14459, np14484, np15257 and np15812 were screened in patient III/2 by PCR/RFLP analysis as well as np14498 by allele specific oligonucleotide hybridization. The presence of the np11778 mutation was confirmed by DNA sequence analysis. Details of the method are described elsewhere [6, 15].

## Results

The family history revealed a 39-year-old man (III/7) who had experienced painless visual loss in both eyes at

the age of 20 years with a visual acuity of 20/400–20/800 in both eyes. He had been diagnosed with LHON in 1973 and showed the typical course of the disease with no recovery of visual function. His mother (II/2) and maternal grandmother (I/2) had poor vision as well, both with early onset of loss of visual acuity. The mother's nonidentical twin sister II/4 and her two daughters (III/11 and III/13) had similar visual disorders; however, no data concerning the age of onset could be obtained in these cases.

Molecular genetic results

Mutation screening revealed the presence of the np 11778 mutation G→A, R340H/ND4 gene) in all family members analyzed. There was no indication for heteroplasmy to the level of the detection limit in the RFLP assay. In addition, we were able to show that secondary mutations at np13708 (G→A, A458 T/ND5 gene) and np4216 (T→C, Y304H/ND1 gene) were present in this family. All other screened mutation sites were excluded in patient III/2.

Three patients were followed over a longer time period.

Case 1 (III/2)

In January 1993 patient III/2 was examined at the age of 31 years. Previously, optic atrophy of unclear etiology had been diagnosed in both eyes. She reported having had poor vision in both eyes since early childhood.

Upon first examination, she had a visual acuity of 20/100 in the right and 20/70 in the left eye with impaired color vision in the Panel D15 test. Visual fields showed paracentral scotomata in both eyes (Fig. 2). The ERG was normal. Pattern-VEP showed delayed P100 latencies for large check sizes and no recordable responses for small check sizes. Fundus examination revealed pale optic discs temporally with otherwise normal findings.
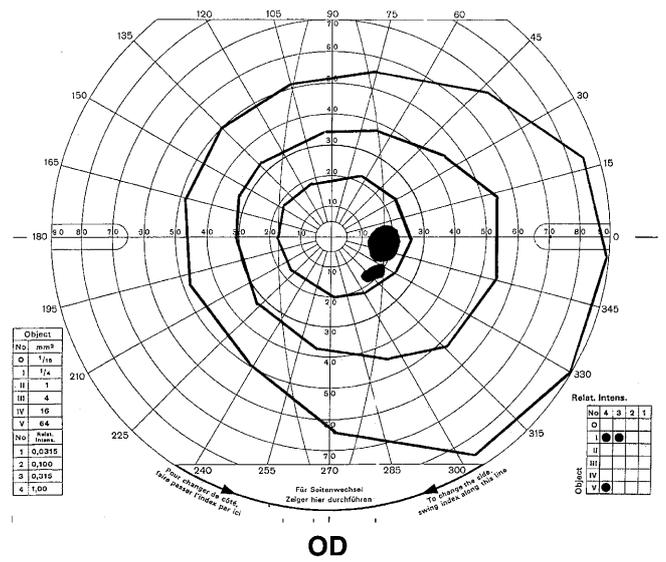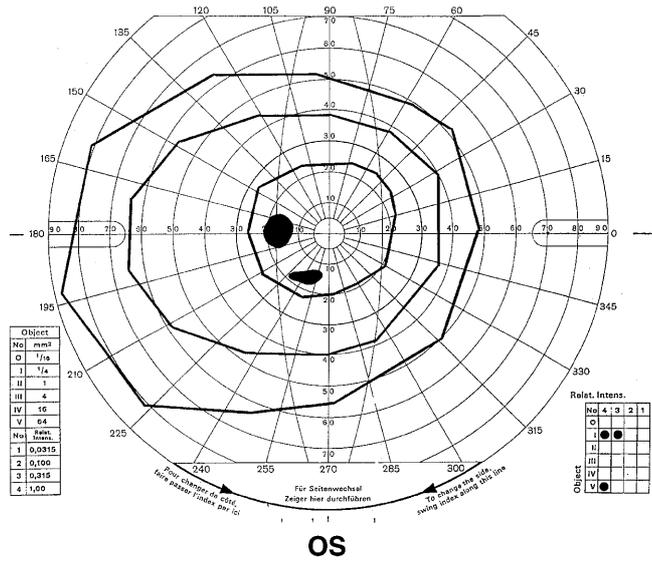
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**Fig. 2** Visual field of patient III/2 (case 1) at the age of 31 showing paracentral scotomata (for target I/3) in both eyes. Poor visual acuity had been reported since early childhood
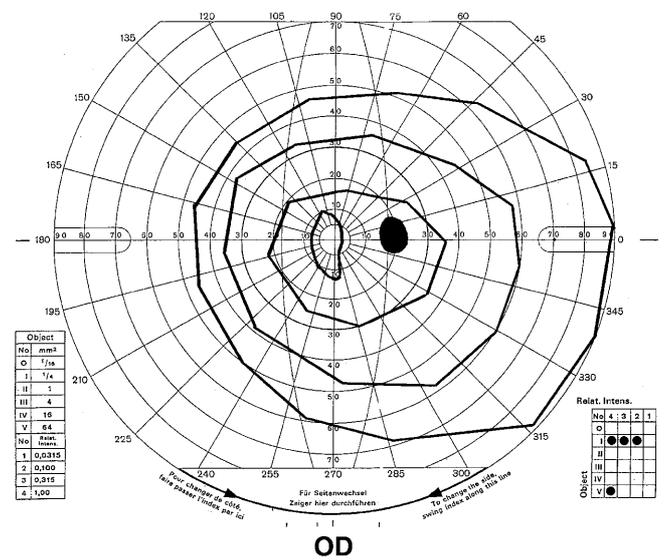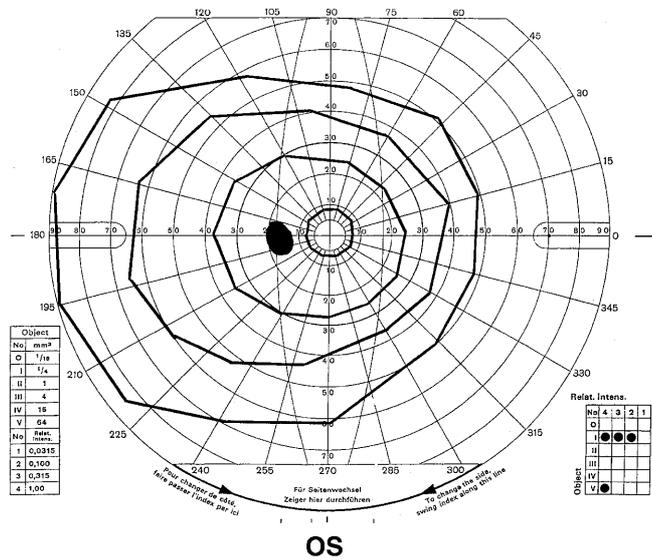
Visual acuity remained unchanged throughout the course of 3 years.

Case 2 (IV/1)

The daughter of patient III/2 had normal vision up to 11 years of age when she suffered acute loss of vision in

January 1994. Upon examination she showed visual acuity of 20/200 in the right and 20/20 in the left eye. Apart from pale optic discs temporally on both eyes fundus findings were normal. The visual field presented a relative central scotoma in the right eye and was normal in the left eye (Fig. 3). The desaturated Panel D15 test revealed mild errors for the right eye. In the course of time visual acuity in the left eye also dropped to 20/200 followed by a slight improvement to 20/100 in both eyes approximately 1 year later and became stable thereafter. The patient's last examination was in March 1997. At follow-up examination visual field tests revealed smaller paracentral and central scotomas but possibly this is due to better cooperation rather than to improvement of visual function. Treatment with Idebenone was performed over a period of 18 months, but no beneficial effect upon visual recovery could be detected.

**Fig. 3** Visual field of patient IV/1 (case 2) at the age of 11 showing a relative paracentral scotoma in the right eye upon first examination. Visual acuity was 20/200 in the right eye. Visual fields as well as visual acuity were normal in the left eye at that time
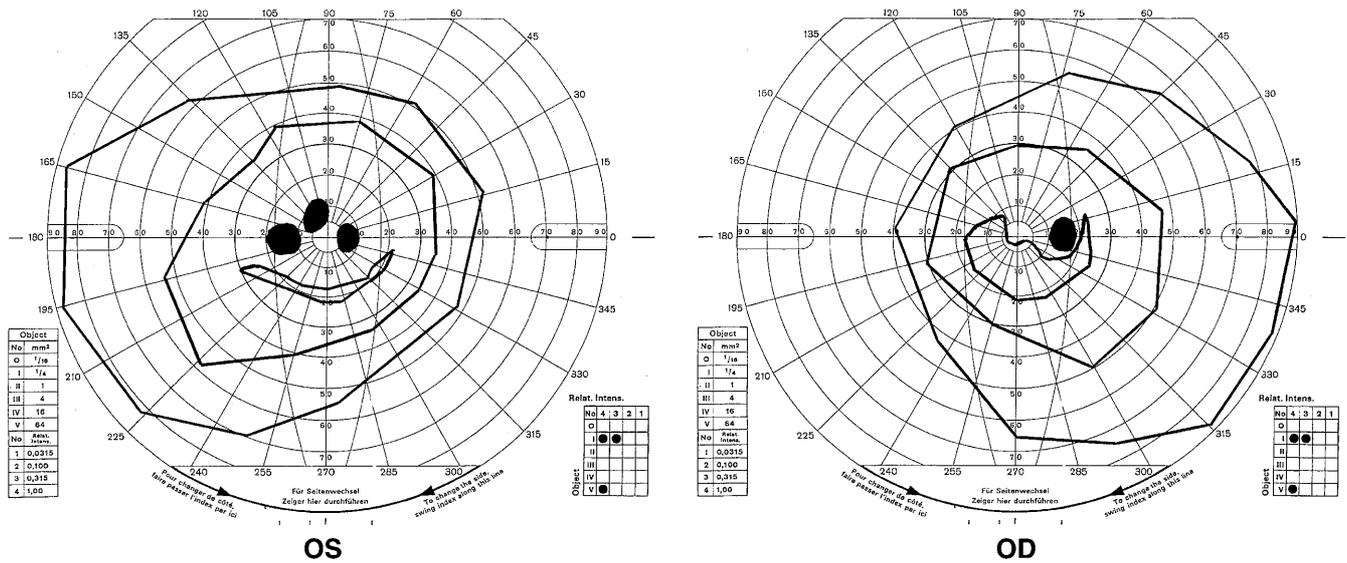


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**Fig. 4** Patient IV/4 (case 3) at the age of 8 years presenting relative central scotomata in both eyes upon first examination. Visual acuity was 20/100 in the right and 20/40 in the left eye

Case 3 (IV/4)

The 8-year-old daughter of an asymptomatic woman (III/6) suffered loss of vision in August 1996 in both eyes. Visual acuity dropped over a period of three weeks to 20/100 in the right and 20/200 in the left eye. The desaturated Panel D15 test showed errors without a typical confusion axis. A relative central scotoma was present in both eyes (Fig. 4). Hyperemic discs and peripapillary teleangiectatic microangiopathy were found in both eyes in an otherwise normal fundus. The young patient was last seen in April 1998 with vision stabilized at 20/200 in both eyes. Ibedenone therapy was initiated in August 1996 but was discontinued after 5 weeks because of vomiting and loss of appetite. There was no indication that Idebenone therapy had had a beneficial effect on the course of the disease.

## Discussion

Leber's hereditary optic neuropathy (LHON) is a strictly maternally inherited disease which results from the presence of defects in the mitochondrial DNA (mtDNA). To date, four primary disease-associated mutations have been identified, namely np3460 (ND1) [10], np11778 (ND4) [27], np14484 (ND6) [11] and np14498 (ND6) [15]. The most frequent mutation is np11778 (ND4), which accounts for 50–70% of all cases of LHON. Penetrance of the disease is 30–50% in males and 5–15% in females. The ratio of affected males to females is 4.2:1 for np11778 cases [19].

This study was carried out on several individuals from a family in which LHON showed considerable deviations from the usual clinical course. The subtype of LHON reported here is linked to a mutation at np11778, has penetrance of over 60% and predominantly affects females instead of males. The only affected male showed the typical course of the disease with loss of vision in his early twenties. Older female patients report that loss of visual acuity occurred in early childhood. In two young girls acute loss of visual acuity was observed at the age of 8 and 11 years, respectively.

The age of onset of severe visual loss can vary considerably, from 6 to 62 years. In 69% of patients visual loss begins between the ages of 11 and 30 years [18, 25]. The mean age of onset in females carrying the np11778 mutation is 26 years [21]. The family reported here is very unusual as in that all effected females suffered visual loss at an age of about 10 years. Visual acuity dropped to 20/200 in both eyes and stabilized at this level. This corresponds to other studies which showed that significant recovery of vision is an exception in patients carrying the np11778 mutation [2, 22, 25]. However, it should be noted that at least for the np11778 mutation, visual recovery is correlated with age of onset [12, 18]. Newman and coworkers reported three patients with significant visual improvement, aged 9, 12 and 15 years at onset of LHON. In contrast, in patients from this family early onset did not correlate with recovery of vision.

Furthermore, the family shows an untypically high number of affected females. Data from a recent multicentric study give a ratio of 4.2:1 for affected males and females with the np11778 mutation [19]. In the present family 8 of 11 females are affected (73%). The overall risk for males in this family is 33% (1/3). The small number of males in the family needs to be taken into consideration when interpreting the overall risk calculation.

In this family the age of onset in females was strikingly low. LHON is still referred to as a disease affecting men in early adulthood. However, ophthalmologists as well as pediatricians must now consider LHON in younger patients of either sex with sudden visual loss.

The underlying reasons why LHON becomes clinically manifest are still unknown. Internal and external environmental factors are thought to initiate or enhance phenotypic expression of the disease [24]. External factors such as heavy alcohol or tobacco abuse must be considered as well as internal factors such as systemic illness or nutritional disorders. All these risk factors could be ruled out in the family presented here. None of the patients examined reported alcohol or tobacco abuse. Environmental toxins or systemic diseases like diabetes could not be detected.

The np11778 mutation is frequently combined with secondary mutations at np13708 and np4216. This association comprises more than a quarter (19/67) of all np11778 families in central European LHON patients [6]. Although it has been argued that the high frequency of this association might result in a cumulative patho-genic effect [10], there is no evidence for more severe clinical symptoms, earlier age of onset and higher penetrance in this group of families [23]. With the exception of the family presented here, ratio of affected males to females in this group is, at 5:1, roughly the same as in families carrying only the np11778 mutation [6].

Attempts to treat the acute phase of the disease with various drugs such as steroids or cyanide antagonists have proven ineffective [8]. Idebenone is a drug that acts on the cerebral metabolism and influences mitochondrial membrane metabolism. A case of marked visual improvement in a 10-year-old boy carrying the np11778 mutation after oral treatment with Idebenone has been reported [20]. In our patients no beneficial effect could be observed. It appears that an effective agent for the prevention and treatment of LHON still needs to be found.

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