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

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/npl1778 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 telangiectasia 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
factor in addition to the primary mutation. An X-linked factor has been proposed, as well as specific male to fe-
male liability. However, these findings remain controver-
sial [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 fe-
males 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 pa-
tients of this family. MtDNA mutation analysis was per-
formed 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 ex-
amined 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 record-
ing of visual pattern evoked potentials (VEP) according to pub-
lished 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

Fig. 1 Pedigree drawing of the LHON family reported in this paper. Squares represent males and circles females. Solid sym-

bols represent subjects with visual loss

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 daugh-
ters (III/11 and III/13) had similar visual disorders; how-
ever, no data concerning the age of onset could be ob-
tained in these cases.

Molecular genetic results

Mutation screening revealed the presence of the np11778 mutation G→A, R340H/ND4 gene) in all family members analyzed. There was no indication for hetero-
plasmy to the level of the detection limit in the RFLP as-
say. 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 peri-
od.

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 im-
paired 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 lat-
encies for large check sizes and no recordable responses for small check sizes. Fundus examination revealed pale optic discs temporally with otherwise normal findings.