

# Leber's Hereditary Optic Neuropathy with Childhood Onset

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**PURPOSE.** To characterize the clinical features of childhood-onset Leber's hereditary optic neuropathy (LHON) as defined by a pathogenic mtDNA mutation and age at onset equal to or less than 10 years of age.

**METHODS.** Fifty-six LHON Italian pedigrees including 180 affected individuals were reviewed, and 14 of 18 patients with childhood LHON were enrolled. LHON was classified as acute bilateral, acute unilateral, slowly progressive, and subclinical, according to disease features. All patients underwent a complete ophthalmic examination and optical coherence tomography (OCT), including retinal nerve fiber layer (RNFL) and optic nerve head analysis (ONH), and were compared with age- and optic disc size-matched control groups.

**RESULTS.** The prevalence of childhood LHON in this case series was 11.5%. Five patients had an acute bilateral course, three an acute unilateral course with subclinical signs in the fellow eye, and six a slowly progressive course. Four of five acute patients with acute bilateral disease experienced visual recovery. Slowly progressive cases presented a better visual acuity and visual field outcome than acute cases. A significant diffuse reduction of RNFL was evident in children with acute LHON compared with the control group, whereas a significant reduction of the temporal quadrant was present in the slowly progressive and subclinical LHON cases. Acute LHON children had a smaller disc area and vertical disc diameter than did the control subjects.

**CONCLUSIONS.** This study systematically characterized for the first time the subgroup of LHON with childhood onset. The peculiar clinical and anatomic features of childhood LHON offer insights for the understanding of LHON's pathophysiology as well as a basis for the differential diagnosis of visual loss in childhood. (*Invest Ophthalmol Vis Sci.* 2006;47:5303-5309) DOI:10.1167/iov.06-0520

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Presented in part at the annual meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, Florida, April 2005.

Submitted for publication May 10, 2006; revised July 7, 2006; accepted September 15, 2006.

Disclosure: **P. Barboni**, None; **G. Savini**, None; **M.L. Valentino**, None; **C. La Morgia**, None; **C. Bellusci**, None; **A.M. De Negri**, None; **F. Sadun**, None; **A. Carta**, None; **M. Carbonelli**, None; **A.A. Sadun**, None; **V. Carelli**, None

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Leber's hereditary optic neuropathy (LHON) is a maternally inherited disease typically leading to a bilateral centrocecal scotoma due to preferential loss of papillomacular bundle nerve fibers.<sup>1</sup> Nearly all patients worldwide carry one of three mitochondrial (mt)DNA pathogenic point mutations at positions 11778/ND4, 3460/ND1, and 14484/ND6, which affect complex-1 subunit genes.<sup>2</sup> More recently, other rare pathogenic point mutations have been described in a minority of patients.<sup>2-5</sup>

Patients with classic LHON experience loss of central vision between 15 and 35 years of age and present an acute/subacute course of the disease that is usually bilateral, frequently with nearly synchronous involvement of the two eyes.<sup>1,2</sup> After reaching a nadir within 6 months, visual loss is usually permanent. However, the prognosis is mutation dependent.<sup>1,2</sup> The 14484/ND6 mutation has the highest rate of spontaneous visual recovery when the age at onset is younger than 20 years. An early age at onset is also a favorable prognostic factor for those carrying the other mutations.

Because the availability of molecular testing and the publication of large series of patients of different ethnic origin, the classic presentation of LHON has widened to include less-typical features. For example, the age at onset of diagnosed patients is considerably more variable, with cases reported in persons between 2 and 80 years of age.<sup>1</sup> Atypical clinical presentation include a slowly progressive course, in which loss of visual acuity continues to deteriorate over a course of more than 8 weeks, and a subclinical course, in which patients report no visual impairment.<sup>6</sup> Very few cases of truly unilateral ocular involvement have been described.<sup>1,6-9</sup>

LHON has only occasionally been reported in children, when visual loss occurred under the age of 10.<sup>1,6,8,10-22</sup> However, probably due to the rarity of the condition, no systematic studies characterizing LHON in childhood are currently available. Furthermore, with very early disease onset, clinicians may face considerable difficulties in differentiating LHON from dominant optic atrophy (DOA), which is typically diagnosed in children younger than 10 years; from optic nerve hypoplasia; or from a variety of unilateral causes of visual impairment, such as amblyopia.<sup>12,23</sup>

After a retrospective reevaluation of all patients with LHON observed by our study group on hereditary optic neuropathies (Department of Neurologic Sciences of the University of Bologna, Bologna, Italy, and Centro Salus, Bologna, Italy) between 1990 and 2004, we recruited for the present study the largest series to our knowledge of patients with LHON with onset before 10 years. We studied these patients to describe the frequency and clinical features of childhood LHON, providing some clues on its classification and the basis for differential diagnosis from other optic nerve diseases presenting in children.

## METHODS

We reviewed all Italian patients with molecularly confirmed diagnosis of LHON referred to our collaborative study group at the Department

of Neurologic Sciences of the University of Bologna and at Centro Salus Bologna between 1990 and 2004. Our historical sample is composed of 56 LHON Italian families with a total of 180 affected individuals. The molecular stratification of our sample shows 35 families carrying the 11778/ND4 mutation (116 patients), 11 families carrying the 3460/ND1 mutation (28 patients), six families carrying the 14484/ND6 mutation (23 patients), two families carrying the 3733/ND1 mutation (7 patients),<sup>3</sup> one family carrying the 14482/ND6 mutation (2 patients),<sup>4</sup> and one family carrying the 14495/ND6 mutation (4 patients).<sup>5</sup> We determined the age of onset of visual symptoms in 157 individuals, and 18 of them had an age at onset equal to or less than 10 years. Fourteen of these were enrolled in the present study, and they were re-evaluated between June 2004 and January 2005. The only exclusion criterion was the presence in one or both eyes of any retinal disease and/or optic nerve disease other than LHON.

All patients underwent a complete ophthalmic examination, including visual acuity measurement, slit lamp observation of the anterior segment, indirect ophthalmoscopy and applanation tonometry. Visual field testing with a perimeter (Humphrey Field Analyzer (Carl Zeiss Meditec, Inc., Dublin, CA) was performed in all patients with good fixation. For evaluation and classification of each visual field, we used the criteria and methodology described in the Optic Neuritis Treatment Trial.<sup>24</sup>

All patients underwent retinal nerve fiber layer (RNFL) thickness measurement and optic nerve head (ONH) analysis by optical coherence tomography (StratusOCT, software version 3.0; Carl Zeiss Meditec, Inc., Dublin, CA). The respective acquisition protocols adopted were RNFL Thickness 3.4 and Fast Optic Disc, as previously reported.<sup>25</sup> For each eye, we studied the mean RNFL thickness (360° measure), temporal quadrant thickness (316°–45° unit circle), superior quadrant thickness (46°–135°), nasal quadrant thickness (136°–225°), and inferior quadrant thickness (226°–315°), all automatically calculated by OCT with the existing software. Only good-quality OCT data as judged by the appearance of the RNFL and the optic disc pictures were used for further analysis. Images with artifacts, missing parts, or of seemingly distorted anatomy were excluded. As regards RNFL measurements, because the position of the circular scan with respect to the optic disc was crucial, we included only images in which the ONH was well centered by the scan. In the case of ONH analysis, if necessary, the manual option was used to correct a displaced ONH margin.

RNFL measurements in patients with childhood-onset LHON were compared with a control group matched for age and ONH size, since both factors have been found to influence the assessment of RNFL thickness by OCT.<sup>25,26</sup> The age- and disc size-matched control group (control group 1) consisted of 35 eyes randomly selected from 35 individuals. A second age-matched control group (control group 2) was used for comparative purposes when evaluating ONH measurements, was matched only for age (and not for ONH size), and was composed of 43 eyes randomly selected from 43 individuals.

Our cases of patients with LHON were classified as “acute” or “slowly progressive” according to the criteria suggested by Nikoskelainen et al.,<sup>6</sup> with modifications concerning the timing of the nadir of visual loss. In fact, we considered the cases as acute when the nadir of visual loss was reached within 6 months and as slowly progressive when visual loss worsened further over the limit of 6 months. A third category, defined as “subclinical” according to Nikoskelainen et al., included those eyes for which the patients never complained of visual impairment, although ophthalmic evidence of optic atrophy was provided.<sup>6</sup>

Details on the tempo and pattern of visual loss were acquired either by direct observation of the patient or from a review of the clinical charts if the patient was at another institution at the time of initial presentation.

This study was approved by the internal board of the Department of Neurologic Sciences at the University of Bologna. All patients gave their informed consent according to the Declaration of Helsinki.

## Statistics

All statistical analyses were performed with commercial software (In-Stat ver. 3a for Macintosh; GraphPad Software, San Diego, CA). For statistical purposes, only one eye, randomly chosen, was evaluated in each patient. Data were compared by one-way analysis of variance (ANOVA), with the Bonferroni post hoc test used when they were sampled from Gaussian distribution (as assessed by the Kolmogorov-Smirnov method); in the case of non-Gaussian distribution, nonparametric analysis of variance (Kruskal-Wallis test with the Dunn multiple comparison post hoc test) was selected.

Prevalence of childhood patients in the different LHON pathogenic mutations was analyzed using the  $\chi^2$  test. Values of  $P < 0.05$  were considered statistically significant.

## RESULTS

Eighteen childhood patients with LHON were identified with an age at onset equal to or less than 10 years of the 157 affected individuals for whom the age at onset was known, representing approximately 11.5% of the sample. Stratifying this cohort of patients by mtDNA genetic defect, we found that 18% (5/28) carried the 3460/ND1, 10.3% (10/97) the 11778/ND4, and 5% (1/19) the 14484/ND6 mutation. Among our childhood cases, two further patients carried the rare mutations 14482/ND6 (1/2) and 3733/ND1 (1/7). No childhood cases were observed in the single family carrying the rare mutation 14459/ND6 (four affected patients) in our case series. This stratification by mutation of our patient's series did not show statistically significant differences, even if a tendency toward a higher frequency of childhood cases with the 3460/ND1 mutation was noted. The 14 subjects who participated in this study were from 10 unrelated pedigrees.<sup>27</sup> Nine patients (six pedigrees) carried the 11778/ND4 mutation, four patients (three pedigrees) the 3460/ND1 mutation and one case the 3733/ND1 mutation. Thus, in two 11778/ND4 families and in one 3460/ND1 family there was a familial recurrence of childhood cases. Overall, eight patients with childhood onset patients showed the features of “acute” LHON: In five of them the disease was typically bilateral, whereas in the remaining three, an atypical unilateral visual loss was detected. In the latter cases, although the visual loss presented in early childhood (before age 5), the disease onset was considered acute because subsequent follow-up did not show any further worsening of visual acuity. Conversely, six patients showed a slowly progressive course (Table 1).

Mean age at last examination and mean age at onset are reported in Table 1. It must be considered that with the exception of two patients seen 1 year after the disease onset, all the others were observed on average  $22.6 \pm 11.7$  years (SD) after onset. Eight of 14 childhood presentations came to us with the incorrect diagnosis of either amblyopia (seven cases) or tapetoretinal degeneration (one case). The remaining six patients, who had a positive familial history for hereditary optic neuropathy, were referred to us with a suspected diagnosis of LHON (three cases) or nonspecific optic neuropathy (three cases).

The ophthalmoscopic feature of childhood patients who had acute bilateral LHON was diffuse optic disc atrophy without microangiopathy (Figs. 1A, 1B) and this was observed in all patients, including a 10-year old girl with a 1-year history of visual loss and no visual recovery. The only acute case with temporal optic atrophy and some evidence of microangiopathy was a 10-year-old boy with recent visual loss (1 year) and early visual recovery.

Childhood patients with acute unilateral LHON had a different presentation from the bilateral cases. The affected eye showed a variable degree of atrophy and microangiopathy (Fig.

TABLE 1. Clinical and Genetic Characteristics of the Study Groups

	Males/ Females	11778/ND4	3460/ND1	3733/ND1	Age at Onset (Mean $\pm$ SD)	Age* (Mean $\pm$ SD)	Visual Acuity (Mean $\pm$ SD)*†	
							Best Eye	Worse Eye
Acute bilateral LHON	4/1	1	3	1	7.4 $\pm$ 3.2	24.6 $\pm$ 15.5	0.33 $\pm$ 0.38	0.1 $\pm$ 0.07
Acute unilateral LHON	3/0	2	1		<5.0	25.6 $\pm$ 15.1	1.0	0.13 $\pm$ 0.02
Slowly progressive LHON	5/1	6			5.6 $\pm$ 0.9	26.5 $\pm$ 12.2	0.67 $\pm$ 0.19	0.45 $\pm$ 0.18

\* At last examination.

† Decimal fraction.

1C), whereas a temporal atrophy of the optic disc, an evident microangiopathy and a mild degree of nerve fiber layer swelling were the most prominent signs in the other eye (Fig. 1D) which was therefore classified as subclinical. These patients will be referred as “subclinical/acute unilateral.”

When LHON had a “slowly progressive” course, optic atrophy was limited to the temporal sector of the optic disc in both eyes with a variable degree of microangiopathy (Figs. 1E, 1F).

Visual loss was worst in acute than in slowly progressive LHON, although four of five patients with childhood acute bilateral LHON experienced visual recovery. This occurred bilaterally in three cases and unilaterally in one case.

Considering all childhood patients with acute bilateral LHON, mean visual acuity was  $0.1 \pm 0.07$  in the worse eye and  $0.3 \pm 0.38$  in the better one. In case of acute unilateral LHON, mean visual acuity was  $0.13 \pm 0.02$  in the affected eye and 1.0 in the apparently unaffected eye. When the course of LHON was slowly progressive, mean visual acuity was  $0.45 \pm 0.18$  in the worse eye and  $0.67 \pm 0.19$  in the better eye.

The visual field examination could be performed in all cases, except those that did not show visual recovery after acute bilateral LHON (three eyes). Acute bilateral and unilateral LHON showed large central scotomas with or without associated paracentral scotomas and with different degrees of fenestration. Slowly progressive and subclinical LHON showed centrocecal scotomas smaller than  $10^\circ$ . There were two exceptions: one acute unilateral case had a centrocecal scotoma smaller than  $10^\circ$  and one slowly progressive case had a paracentral defect other than a centrocecal scotoma (Fig. 2).

RNFL thicknesses, as measured by OCT, are reported in Table 2. The most evident changes were a diffuse reduction of the RNFL in cases with acute LHON, where all quadrants were significantly thinner than in the control group. Patients with slowly progressive LHON showed a significant reduction in the temporal quadrant and a mild, not statistically significant, reduction in the inferior one.

Eyes with a subclinical course had an RNFL pattern similar to that in slowly progressive LHON, characterized by a reduction (although not statistically significant) of the temporal quadrant and, to a lesser extent, of the inferior one. Figure 3 shows the typical double-hump pattern of RNFL thickness with a peak in inferior and superior quadrants in all groups considered in Table 2.

According to ANOVA, ONH analysis by OCT disclosed a statistically significant difference in the disc area and in the vertical diameter between groups (Table 3). Subjects with acute LHON showed a smaller disc area than did the control subjects and a smaller vertical disc diameter than did the control subjects and patients with and slowly progressive disease (Table 3).

## DISCUSSION

This study describes and differentiates the clinical features of childhood-onset LHON in a case series of 14 patients from 10

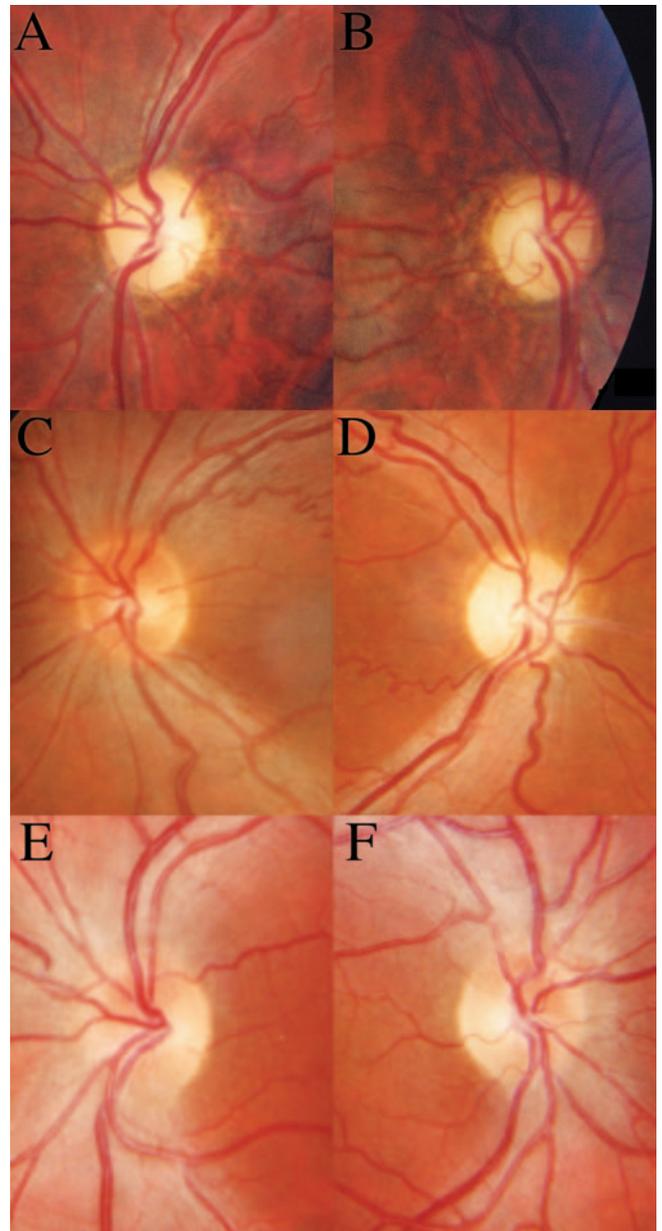
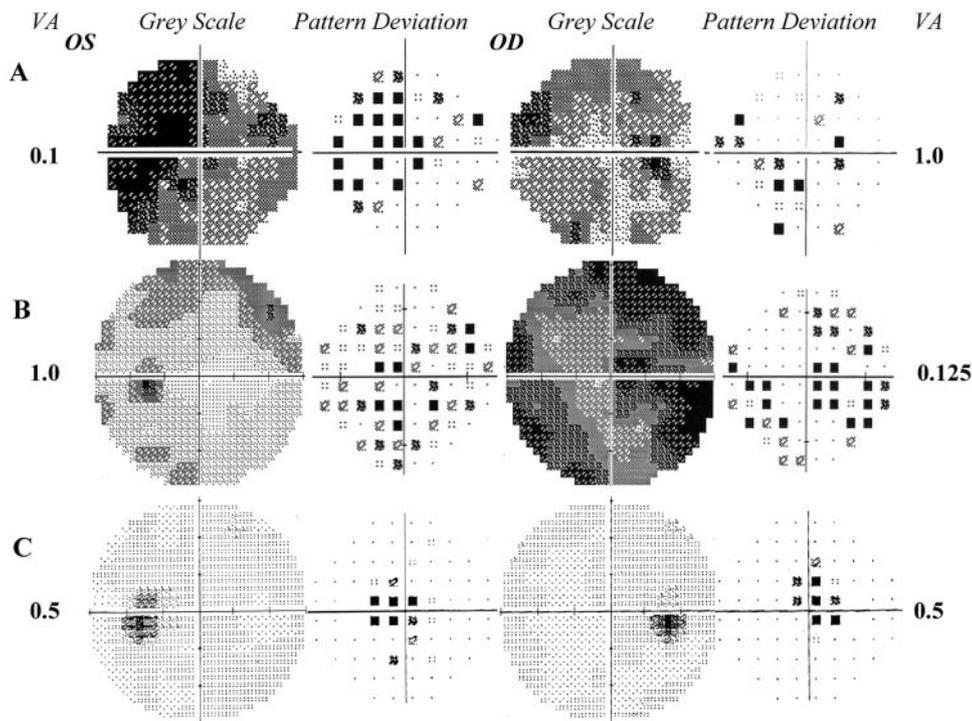


FIGURE 1. Color fundus pictures of the right and left eyes. Acute bilateral LHON: Diffuse atrophy of the optic discs is evident without microangiopathy (A, B). Acute unilateral LHON: The affected eye (C) shows optic disc atrophy, more evident in the temporal quadrant, whereas the fellow eye (D), classified as subclinical, reveals temporal atrophy of the optic disc, a mild degree of microangiopathy, and nerve fiber layer swelling as the most prominent signs. LHON with a slowly progressive course: Temporal optic atrophy with mild nerve fiber layer swelling of the other quadrant is detected in both eyes (E, F).



**FIGURE 2.** Full-threshold, 24° and 30° visual fields of the right optic nerve (OD), left optic nerve (OS), and visual acuity (VA) of the patients depicted in Figure 1. (A) Visual field and visual acuity in acute bilateral LHON. A temporal defect and a small fenestration of centrocecal scotoma were evident in the right eye and a large fenestration of centrocecal scotoma and nasal defect were noted in the left. (B) Acute unilateral LHON. Visual fields showed a mild diffuse defect and small centrocecal defects in the left eye, with a subclinical course, and a severe diffuse defect, enlarged blind spot, and nasal defect in the right, with an acute course. (C) Slowly progressive LHON. Visual fields revealed a centrocecal scotoma smaller than 10° in both eyes.

unrelated families. We defined childhood-onset LHON as onset at age  $\leq 10$  years or younger. We found some remarkable differences from adult-onset presentation and identified three main subcategories indicated as acute bilateral LHON, slowly progressive LHON, and subclinical/acute unilateral LHON, mostly in accordance with some seminal distinctions made by Nikoskelainen et al.<sup>6</sup>

Compared with the well-established clinical features of adult-onset LHON, childhood-onset disease was of a milder form. In patients with acute bilateral LHON the incidence of visual recovery (4/5 patients, 7/10 eyes) was higher than that usually reported in adult-onset LHON whose incidence ranges between 4% and 58%, depending on the common pathogenic mutation considered.<sup>1</sup> In regard to the two rare mutations at positions 14482/ND6 and 3733/ND1 included in our cohort, (despite the limited number of cases reported to date), it appears that there is a high probability of vision recovery similar to that seen in the benign 14484/ND6 mutation.<sup>3,4</sup> In cases that presented as acute unilateral, the worse eyes had a mean visual acuity of 0.13, whereas the subclinical contralateral eyes all had normal visual acuities (1.0; Table 1). The slowly progressive cases, which seem to be a peculiar feature of childhood-onset LHON, maintained a good final visual outcome compared with the other childhood cases. Furthermore, the visual field evaluation showed in most cases either fenestration of a centrocecal scotoma or a centrocecal scotoma smaller than 10°. This confirms the better course and prognosis of childhood-onset LHON. Overall, these data support the concept that the prognosis of childhood LHON is better than in adults for all mutations.

The second observation drawn from this study is that acute childhood LHON most closely mimics adult-onset LHON. In this presentation, there is a rapid early loss of the papillomacular bundle followed by complete optic atrophy after disease onset, with or without the possibility of some degree of visual recovery (Figs. 2A-C, Fig. 3). In contrast, the slowly progressive and subclinical LHON childhood cases tended to be mostly affected only on the inferotemporal quadrants, with relative preservation of fibers in the other sectors (Fig. 3). This feature

was also observed in the fundus photographs, where some degree of swelling of the superior and partially of the inferior arcades was evident (Figs. 2D-F). Further follow-up of these cases will elucidate whether the maintenance of RNFL thickness is mostly due to immediate swelling of fibers that will be lost over time or to a true preservation of healthy, functioning axons. This clinical course in childhood LHON is unusual and in several respects is reminiscent of the natural history of DOA.<sup>2,28</sup> DOA seldom presents with funduscopic evidence of nerve fiber swelling in the superior and inferior arcades. Yet in DOA, the optic atrophy is first seen on the temporal side of the optic disc, involving primarily the papillomacular bundle, in a pattern similar to that seen in LHON.<sup>1</sup> Incidentally, the so-called unilateral cases in our childhood onset cohort were always associated with a subclinical involvement of the fellow eye<sup>7</sup> showing the unusual feature of a very asymmetric severity of the optic neuropathy between the eyes. The cause of such asymmetry remains unexplained.

A third intriguing result of this study concerns the size of the ONH. The most striking observation is that the childhood LHON cases with acute onset presented a significantly smaller disc area and vertical diameter of ONH than do control subjects. By contrast, the slowly progressive LHON cases showed no differences of disc area and vertical and horizontal diameters compared with control subjects. We also found that a smaller optic disc area in adult LHON is a negative prognostic factor influencing final visual outcome. (Bellusci C et al. *IOVS* 2006;47:ARVO E-Abstract 756). All considered, these results provide the first evidence that the anatomic size of the optic disc may influence the clinical expression particularly regarding the tempo, or severity of LHON.<sup>8,29</sup>

The age-dependence of LHON is one of the most remarkable and as of yet unexplained features of this disorder. The availability of molecular testing has greatly enhanced the accuracy of LHON diagnosis and broadened the range of positively identified cases. Thus, the age of onset is also now accepted to be more variable than initially thought, including both childhood and late-onset cases.<sup>1</sup> We found that childhood-onset LHON in our case series accounts for 11.5% of all LHON-

TABLE 2. RNFL Thickness, as Measured by OCT

	Average	P†	Temporal	P†	Superior	P†	Nasal	P†	Inferior	P†
Acute LHON (n = 8)*	56.28 ± 9.58	<0.001	31.75 ± 7.21	<0.001	67.88 ± 15.23	<0.001	54.00 ± 11.26	<0.01	69.63 ± 14.87	<0.0001
Slowly progressive LHON (n = 6)	90.48 ± 6.89	<0.05	38.50 ± 5.89	<0.01	124.00 ± 8.94	NS	88.00 ± 6.96	NS	110.50 ± 18.35	NS
Unilateral subclinical LHON (n = 3)	91.94 ± 11.48	NS	44.33 ± 5.86	NS	126.33 ± 19.35	NS	84.33 ± 8.50	NS	112.67 ± 17.62	NS
Control group 1 (n = 35)	103.77 ± 8.4	—	72.88 ± 10.2	—	129.8 ± 11.1	—	80.02 ± 15.1	—	131.8 ± 14.0	—
ANOVA	P < 0.0001	—	P < 0.0001	—	P < 0.0001	—	P < 0.0001	—	P < 0.0001	—

Data are in mean micrometers ± SD.

\* One randomly selected eye of bilateral cases and the affected eye of unilateral cases are included.

† Dunn multiple comparison post hoc test compared with control group results.

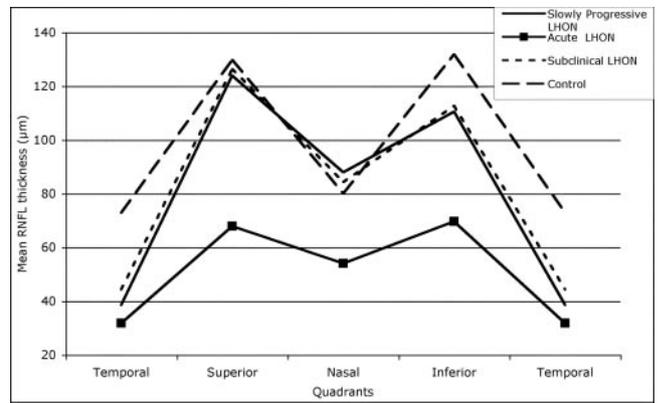


FIGURE 3. RNFL thickness in each quadrant of slowly progressive, acute, and subclinical Leber's hereditary optic neuropathy (LHON), compared to that in the control group. Compared with the control group, the eyes with acute LHON showed a significantly thinner RNFL in all quadrants. Patients with slowly progressive LHON presented a significant reduction of the temporal quadrant and a not statistically significant reduction of the inferior quadrant. Eyes with a subclinical course showed a reduction (although not statistically significant) of the temporal quadrant and, to a lesser extent, of the inferior quadrant.

affected patients. Early-onset optic atrophy, as well as a slower and more limited progression, characterizes DOA, and some similarities with this different form of mitochondrial optic neuropathy have also been found in our series namely, the slowly progressive and subclinical categories. We may speculate that this overlap in the clinical course of optic neuropathy reveals similarities in some of the pathophysiological mechanisms responsible for childhood LHON and DOA. We also noted some familial aggregation of childhood LHON cases in our series (four families with at least two cases) suggesting that certain supplementary genetic factors may induce the early onset of optic neuropathy. The other noticeable feature in childhood LHON is its extremely asymmetric clinical expression in patients with the subclinical/acute unilateral form of the disease. This denotes an asynchronous timing in the pathologic mechanisms underlying the optic neuropathy, which may be explained by a particularly benign form of LHON. In fact, all our cases showed a very high rate of visual recovery. Under this scenario, the pathologic process does not reach the necessary threshold in both eyes, sparing partially one eye from the progression through the full-blown acute phase.

The remarkably benign course of childhood LHON shown by this study corroborates the general notion that an early age at onset for LHON is a favorable prognostic factor for visual recovery. However, this age-related effect remains to be explained. Two main factors seem to dictate this benign course of childhood LHON. First, there is slow rate of nerve fiber loss and good final visual outcome in the subgroups of slowly progressive LHON cases as opposed to the classic acute LHON typically seen in adults. Second, there is a higher rate of spontaneous improvements in visual acuity in the subgroups with the childhood acute loss of vision (bilateral or unilateral) compared with the classic acute LHON of adults. In both instances the young age at onset seems to be the relevant factor. An asynchronous loss of axons seems to characterize the slowly progressive cases, whereas a higher rate of maintained axonal viability probably underlies the visual recovery in the acute cases. We can consider how age may affect these mechanisms that can impact axonal degeneration, especially in regard to synchronization of the pathologic process. For example, impairment of organellar transport in axons, possibly due to energy shortage and/or pathologic fission/fusion of the mitochondrial network, may interact with the efficiency of myelin

TABLE 3. Optic Nerve Head Analysis of the Study Groups

	Disc Area (mm <sup>2</sup> )	Vertical Diameter (mm)	Horizontal Diameter (mm)
Acute LHON (n = 8)*	1.71 ± 0.28†	1.43 ± 0.11‡	1.40 ± 0.14
Slowly progressive LHON (n = 6)	2.04 ± 0.16	1.65 ± 0.16§	1.50 ± 0.10
Unilateral subclinical LHON (n = 3)	1.91 ± 0.08	1.5 ± 0.16	1.38 ± 0.14
Control group 2 (n = 43)	2.02 ± 0.28	1.67 ± 0.11	1.52 ± 0.13
ANOVA	P = 0.02	P = 0.0001	NS

Data are the mean ± SD.

\* One randomly selected eye of bilateral cases and the affected eye of unilateral cases are included.

† P < 0.05 with the Bonferroni multiple comparison post hoc test with respect to the control group.

‡ P < 0.001 with the Bonferroni multiple comparison post hoc test with respect to the control group.

§ P < 0.01 with the Bonferroni multiple comparison post hoc test with respect to acute LHON.

turnover, leading to axonal swelling and abnormalities in retinal and ONH vascularization.<sup>2</sup> There is histopathologic evidence that in LHON some still viable but hypomyelinated or demyelinated axons persist after the acute phase, and the state of myelination may be relevant in the cascade of events in LHON pathophysiology.<sup>2</sup> Thus, age is probably relevant to the state of axonal myelination and efficiency of myelin turnover, which are known to be closely correlated with the number of mitochondria and energy dependence of axons, as well as with axonal diameter.<sup>30</sup> The remyelination of partially denuded but still viable axons has been proposed as one of the possible mechanisms underlying the capability to recover visual acuity either spontaneously or during treatment, even years after the onset of the optic neuropathy, and this recovery may be more efficient at a younger age.<sup>2</sup>

In conclusion, our study describes the peculiar clinical features of childhood LHON and differentiates these from the classic adult condition. Furthermore, we present different clinical subgroups of LHON, which may help to understand the underlying pathophysiology of this mitochondrial optic neuropathy. Finally, the understanding of such mechanisms may also help to differentiate these cases from other forms of inherited optic neuropathy in childhood such as DOA or unilateral cases of visual impairment like amblyopia.

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