Childhood-Onset Leber Hereditary Optic Neuropathy—Clinical and Prognostic Insights

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Leber hereditary optic neuropathy (LHON: OMIM#535000, ICD-10: H47.2, ORPHA104) is an important cause of blindness in the young adult male population with an estimated prevalence of 1 in 31,000 to 1 in 50,000.[1–4] It is a maternally inherited disorder, and 3 common mitochondrial DNA (mtDNA) point mutations, m.3460G>A (*MT-ND1*), m.11778G>A (*MT-ND4*), and m.14484T>C (*MT-ND6*), all affecting complex I subunits of the mitochondrial respiratory chain, account for approximately 90% of all cases.[5] LHON is characterized by visual loss that has a marked sex bias and incomplete penetrance with approximately 50% of male carriers becoming affected compared with approximately 10% of female carriers, albeit with wide inter- and intrafamilial variations.[6,7]

The classical course of the disease is clinically characterized by subacute, painless profound loss of central vision affecting both eyes simultaneously or sequentially within weeks to months.[8] Visual loss worsens over a period of 3 to 6 months with an expanding centrocecal scotoma and increasing pallor of the optic disc. One year after disease onset, most patients entering the chronic stage will have pronounced central visual loss that usually quali es them to be registered as legally blind (de ned in Italy 'as a visual acuity worse than 1/20 decimals and in the UK vision worse than 3/60').

Most asymptomatic individuals carrying LHON mtDNA mutations become symptomatic between 15 and 35 years

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of age, but the reported age of onset ranges from 2 to 87 years.[9] The peak age of onset in men has been recently defined between 14 and 26 years with a median age of 20 years compared with a later median age of 30 years in women.[10] Atypical disease onset before the age of 12, referred to as childhood-onset LHON, has been reported in several studies,[8,11–23] with this group representing 8% to 10% of the total LHON population.[10,21,22] The male bias is maintained with a male:female ratio between 2:1 and 6:1. However, for those affected before the age of 5, there is a similar proportion of affected males and females.[10] The distribution of the 3 primary LHON mtDNA mutations is comparable with adult LHON with the m.11778G>A mutation accounting for 48% to 64% of cases.[10,21,23–25] Childhood LHON is distinct from the adult form of the disease with a better visual prognosis and a more varied clinical presentation, which can be insidious, subclinical, slowly progressive, and in some cases unilateral.[18,21,22,24,26–32] The atypical age of onset and nonclassical patterns of visual loss frequently result in significant diagnostic delays with initial misdiagnoses of optic neuritis, compressive optic neuropathy, and functional visual loss being the most common.

In the current study, we have further defined the natural history of childhood-onset LHON in a large cohort of affected children at various stages of visual maturation, and we propose a classification system based on both the presumed age of onset and the pattern of visual loss.[33] The structural parameters of the optic nerve were also correlated with the pattern of visual loss and the final visual outcome.

PATIENTS AND METHODS

This study included patients with LHON with disease onset ≤12 years of age and a confirmed molecular diagnosis (m.3460G>A, m.11778G>A, or m.14484T>C) from Italy or the United Kingdom.[21,22] We have adopted this age cutoff for childhood-onset LHON to clearly differentiate this subgroup from the more typical disease course seen in patients between the ages of 15 and 35 years.[34] The main exclusion criteria were the presence of associated retinal diseases and/or optic nerve diseases other than LHON. The clinical records of eligible patients were reviewed retrospectively for the extraction of relevant data. When feasible, patients were re-evaluated in clinic to gain more longitudinal data about the chronic phase of the disease. This study had the relevant institutional approval and complied with the Declaration of Helsinki. Informed consent was obtained from all participants.

Details about the timing and pattern of visual loss were obtained from the clinical records and, in some cases, by interviewing patients or their guardians. Availability of the presumed age of onset of visual loss and final visual acuity (VA) was a prerequisite for patient inclusion in the study cohort. To categorize the presumed age of onset and the pattern of visual loss, the following questions were considered when assessing the retrieved historical data or when interviewing the patient or their guardians:

1. Was the onset of visual loss sudden? Can you remember a specific point in time when you became aware or suspected poor vision?
2. Was the visual loss only reported or detected by a teacher at school or incidentally by an optometrist/orthoptist/physician during a routine examination?
3. Was an eye examination specifically requested for ocular complaints of strabismus?

On the basis of the data gathered, we first defined the following age groups at the time of diagnosis, based on the stage of visual maturation and biological development, and the methods of VA assessment:[35]

1. Group 1 (<3 years of age): Ongoing visual development. Children are preverbal and the assessment of impaired VA is based on the inability to fix and follow subnormal gratings of preferential looking for age and ocular misalignment. Toddlerhood stage.
2. Group 2 (≥ 3 to <9 years of age): Ongoing visual development. Children can perform a chart vision test. Early/middle stage.
3. Group 3 (≥9 to ≤12 years of age): Full visual development. Children can perform a chart vision test. Preadolescent/adolescent stage.

Patients were further stratified based on the pattern of visual loss:

1. Subacute Bilateral: the onset of visual loss was clearly subacute, similar to the classical adult form of LHON. The children reported a decrease in their vision and/or visual difficulties were reported by their parents or relatives.
2. Insidious Bilateral: the onset of visual loss was not well defined (insidious). The visual loss was frequently not detected by the immediate family, being picked up on visual screening during a routine eye examination or at school during class or sport activities.
3. Unilateral: this group includes patients who reported symptomatic visual loss only in 1 eye in childhood (unilateral involvement that may be either subacute or insidious). This group was further subclassified based on whether the disease remained unilateral (monocular); or the second eye became involved in childhood, but subclinically; or it became involved subacutely when the patient was ≥15 years old.

- Second no involvement (ie, monocular). The second eye has remained unaffected to date with normal functional (both VA and visual fields [VF]) and structural parameters (ie, no pallor of the optic nerve and normal retinal nerve fiber layer [RNFL] and ganglion cell layer [GCL] thickness on optical coherence tomography [OCT] imaging).

- Second subclinical. The second eye was subclinically involved during childhood. The patient was asymptomatic in that eye with no complaints of visual loss. Ophthalmologic examination indicated mild functional damage with VA between 0.8 and 1.0 Snellen decimals or a small central or paracentral scotoma on VF testing. There were only mild structural pathologic changes with temporal optic disc pallor, temporal RNFL thinning, and/or macular GCL thinning on OCT imaging.
- Second subacute ≥15 years of age. The second eye developed the classical subacute visual loss observed in adult patients with LHON.

4. Subclinical Bilateral: both eyes had subclinical involvement as previously defined.
5. Slowly progressive: the documented progression of visual loss lasting >6 months from the onset and not considering the presumed age of onset.

Ophthalmologic phenotyping included: (1) assessment of VA, (2) orthoptic evaluation, (3) slit-lamp biomicroscopy, (4) intraocular pressure measurement, (5) indirect ophthalmoscopy, (6) VF testing (Humphrey Field Analyzer, protocol SITA Standard 30-2; Zeiss), and (7) high-resolution OCT imaging (DRI Triton SS-O4 CT device; Topcon). VA was assessed by measuring the best-corrected VA in Snellen decimals, except for preverbal children whose visual capacity was determined as previously described.

VA recovery was defined as a change of 2 lines or more on the ETDRS (Early Treatment Diabetic Retinopathy Study) chart or from off-chart to on-chart vision after the initial loss of vision in children ≥9 years old.[22] In younger children, an improvement of best-corrected VA was labeled as recovery only if its magnitude was greater than what would be expected from normal visual maturation.

OCT protocols included the evaluation of peripapillary RNFL thickness and GCL segmentation analysis at the macula (with GCL defined as the thickness from the inner boundary of the GCL to the outer boundary of the inner plexiform layer). Only high-quality scans, defined as scans with signal strength ≥7 without RNFL artifacts, and with the absence of segmentation failure, were used for analysis. The images were obtained using a 3-dimensional wide scan protocol with a size of 12 × 9 mm consisting of 256 B-scans, each comprising 512 A-scans. Peripapillary RNFL thickness was measured using a 360° 3.4-mm-diameter circle scan with thicknesses measured. Segmentation analysis of the macula measured across 6 sectors of the 6-mm-diameter circular annulus centered on the foveal included GCL.

For those patients with strabismus, the chronological relationship between the onset of strabismus and visual loss from LHON was also analyzed. Information was collected about a family history of amblyopia, strabismus, and other matrilineal family members becoming affected with LHON when ≤12 years old.

– . . . . . Statistical analysis was performed using SPSS version 26.0 (SPSS Inc, IBM). We carried out the data analysis first with the combined UK and Italian patient cohort and then with the Italian cohort alone. In the UK cohort, clinical and VA parameters were used for the analysis. In the Italian cohort, VF and OCT parameters were also available and they were analyzed separately.

As defined earlier, participants were stratified based on the presumed age of onset (groups 1, 2, and 3). The Anderson-Darling and/or Kolmogorov-Smirnov tests were used for the UK and Italian cohorts to determine if VA was normally distributed. As the data were not normally distributed, Mood's median (nonparametric) test was performed. Patients were also subclassified based on whether they achieved a final VA ≥0.5 decimals. For VA in group 1 (<3 years of age), the Insidious Bilateral and Insidious Unilateral groups were compared with the Mann-Whitney test.

Categorial clinical variables for groups 1, 2, and 3 were analyzed with the χ^2 test (eyes and patients). As above, we performed this statistical test on these 3 groups and the Insidious Unilateral group.

As part of our secondary analysis on the Italian cohort, the normality tests (Anderson-Darling and/or Kolmogorov-Smirnov) were performed on the following variables: VA, mean deviation (MD) from VF testing and RNFL and GCL measurements from OCT imaging. VA and the thickness of the RNFL and GCL did not follow a Gaussian distribution, and the data were analyzed using Mood's median test. As MD was normally distributed, a 1-way analysis of variance was applied with the Tukey method for multiple comparisons. Group 1 and the Insidious Unilateral group were also compared.

Lastly, we performed inferential statistics on VA, MD, RNFL, and GCL measurements to compare group 1 with the Insidious Unilateral group. The statistical models developed relied on the distribution of these 4 parameters. The inferential statistics performed were the Mann-Whitney test for VA, RNFL, and GCL measurements, and the unpaired 2-sample t-test for MD.

RESULTS

Data were available for 81 patients (65 families) with disease onset ≤12 years old: 55 patients (41 families) from the Italian cohort and 26 patients (24 families) from the UK cohort. Patients were grouped according to the predefined classifications (Supplemental Tables 1 and 2). A total of 68 patients were stratified based on the presumed age of onset of visual loss, excluding patients with unilateral involvement (n = 9) and those with subclinical bilateral involvement (n = 4), which were analyzed based on the pattern of visual loss due to their atypical presentations:

TABLE 1. Demographic and Genetic Characteristics of Study Cohort Grouped According to the Age of Onset of Visual Loss

	Group 1 (<3 y)	Group 2 (≥3 to <9 y)	Group 3 (≥9 to ≤12 y)
Patients/eyes	14/28	27/54	27/54
M:F	13:1	2:1	3.5:1
Mean age at onset ± SD (y)	—	6.4 ± 1.5	10.8 ± 1.2
Mean age at last examination ± SD (y)	36.3 ± 17.6	23.0 ± 14.3	23.6 ± 13.8
Pathogenic variant, number of patients (%)/families			
m.11778G>A/*MT-ND4*	8 (53.3)/6	11[c] (39.3)/11	16 (59.3)/16
m.3460G>A/*MT-ND1*	2[a] (13.3)/2	5 (17.9)/5	6 (22.2)/6
m.14484T>C/*MT-ND6*	4[a] (26.7)/3	10 (35.7)/9	4 (14.8)/4
Rare mutation, number of patients (%)	1[b] (6.7)	2[c,d] (7.1)	2[e] (3.7)

[a]One Italian patient with 2 pathogenic variants (m.3460G>A/*MT-ND1* and m.14484T>C/*MT-ND6*).
[b](m.13621C>T/*MT-ND5*).
[c]One UK patient with 2 pathogenic variants (m.5697A>G/*MT-TN* and m.11778G>A/*MT-ND4*).
[d](m.3733G>A/*MT-ND1*).
[e]One Italian patient with a combination of 2 variants (m.14258G>A/*MT-ND6* and m.14582A>G/*MT-ND6*).

- Group 1 (<3 years): 14 patients (20.6%)
- Group 2 (≥3 to <9 years): 27 patients (39.7%)
- Group 3 (≥9 to ≤ 12 years): 27 patients (39.7%)

The entire combined cohort of 81 patients was stratified based on the pattern of visual loss:

- Subacute Bilateral: 54 patients (66.7%)
- Insidious Bilateral: 14 patients (17.3%)
- Unilateral: 9 patients (11.1%)
- Subclinical Bilateral: 4 patients (4.9%)

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TABLE 2. Visual Acuity at Last Examination Grouped According to the Age of Onset of Visual Loss. Bold values indicates statistically significant data.

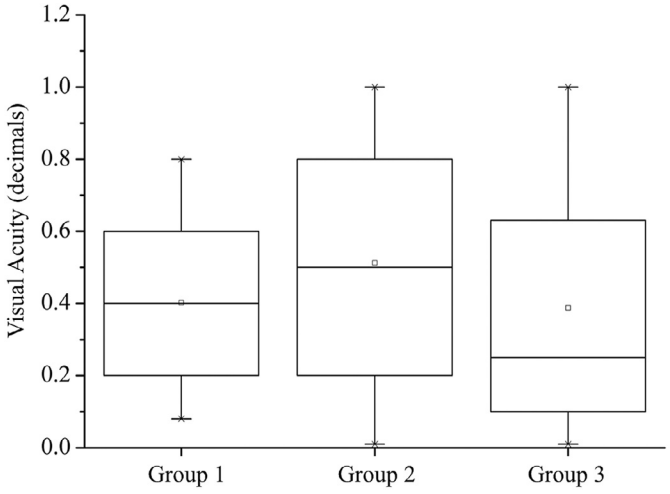
	Group 1 (<3 y)	Group 2 (≥3 to <9 y)	Group 3 (≥9 to ≤12 y)	χ^2; *P* Value
Patients/eyes	14/28	27/54	27/54	—
VA (Snellen decimals), median (IQR)	0.40 (0.40)	0.50 (0.63)	0.25 (0.53)	1.60; 0.450[a]
Patients with at least 1 eye recover (%)	—	23 (85.2)	21 (77.8)	0.49; 0.484[b]
Eyes recover (%)	—	45 (83.3)	35 (64.8)	**4.82; 0.028**[b]
Patients with VA ≥0.5 in at least 1 eye (%)	9 (64.3)	16 (59.3)	16 (59.3)	0.12; 0.943[b]
Eyes with VA ≥0.5 (%)	13 (46.4)	28 (51.8)	22 (40.7)	**12.79; 0.005**[b]

IQR = interquartile range, VA = visual acuity.
[a]Mood's median test: VA (response) vs groups (factor).
[b]Pearson χ^2 test for association.

TABLE 3. Proportion of Patients With Strabismus According to Groups.

	Group 1 (<3 y), Insidious Bilateral	Insidious Unilateral	Group 2 (≥3 to <9 y)	Group 3 (≥9 to ≤12 y)
Number of patients (%)	3 (21.4)	9 (100)	2 (7.4)	2 (7.4)
Mean VA in the deviated eye ± SD	0.16 ± 0.09	0.16 ± 0.20	0.35 ± 0.21	0.09 ± 0.01
Mean VA in the nondeviated eye ± SD	0.33 ± 0.14	0.76 ± 0.34	0.71 ± 0.12	0.66 ± 0.19

VA = visual acuity.



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only 1 patient experiencing visual recovery. The mean VA of the second subclinical eye was 0.81 ± 0.18.

Strabismus. The proportion of patients with strabismus was 21.4% in group 1, 7.4% in group 2, and 7.4% in group 3 (Table 3). All 9 patients with unilateral involvement initially presented with a strabismus. In group 1, 8 of 14 patients were treated for amblyopia in early infancy with patching without any bene□ts. Of the 16 patients with strabismus, 13 presented with an exotropia and 3 with an esotropia. The mean VA (0.18) in the strabismic eyes was overall lower than the nonstrabismic eyes (0.66), and the same trend was observed for the individual groups (Table 3).

Functional and structural relationship in the group of Italian patients

The VA analysis in Italian patients re□ected the cumulative results of the combined Italian and UK cohorts, with group 2 achieving the best visual outcome with a signi□cantly better VA at last examination compared with group 3 (Supplemental Table 3 and Figure 2). Patients in group 1, Insidious Bilateral, had a signi□cantly better VA compared with those in group 3, and a trend toward a worse VA compared

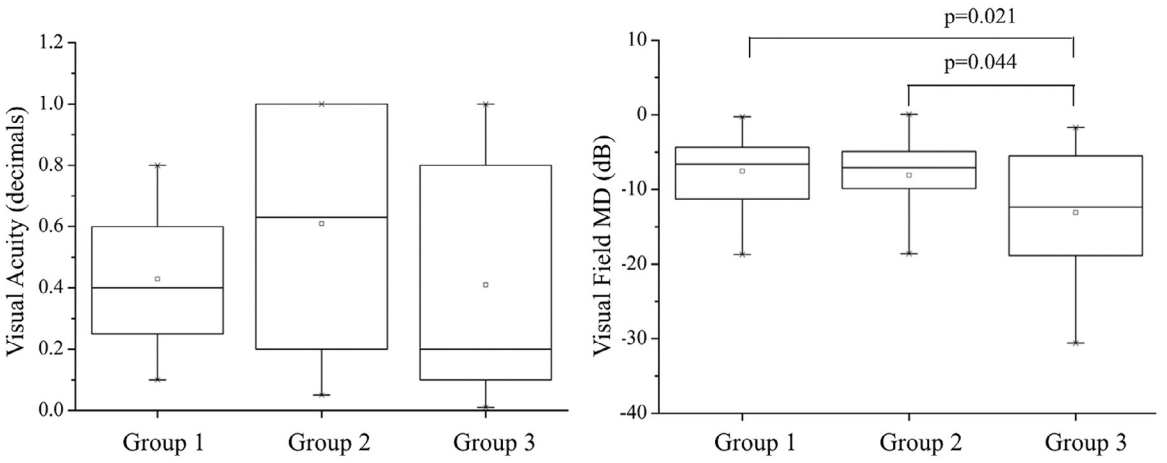


TABLE 4. Ophthalmologic Findings of Italian Patients at Last Examination Grouped According to the Age of Onset of Visual Loss. Bold values indicates statistically significant data.

	Group 1 (<3 y)	Group 2 (≥3 to <9 y)	Group 3 (≥9 to ≤12 y)	χ^2; *P* Value
Patients/eyes	11/22	14/28	17/34	
Visual field MD (dB), mean ± SD	−7.54 ± 4.75	−8.08 ± 4.93	−13.07 ± 9.11	**4.73; 0.012**[a]
Average RNFL thickness (μm), median (IQR)	84.5 (40.0)	58.0 (23.0)	45.0 (24.5)	5.63; 0.060[b]
Average GCL thickness (μm), median (IQR)	43.3 (8.7)	46.8 (11.4)	43.3 (4.5)	**4.46; 0.036**[b]

GCL = ganglion cell layer, IQR = interquartile range, MD = mean deviation, RNFL = retinal nerve fiber layer.

[a]Analysis of variance (*F;p*) and Tukey's test groups' comparison: MD (response) vs groups (factor): group 1 vs group 2, *P* = .967; group 1 vs group 3, *P* = .021; group 2 vs group 3, *P* = .044.

[b]Mood's median test: RNFL and GCL (response) vs groups (factor).

with those in group 2 (Supplemental Table 3). Insidious monocular patients had a signi□cantly worse visual prognosis compared with those in group 1 in the □rst affected eye (VA: 0.13 ± 0.22; $P = .004$), with no eyes achieving VA ≥0.5.

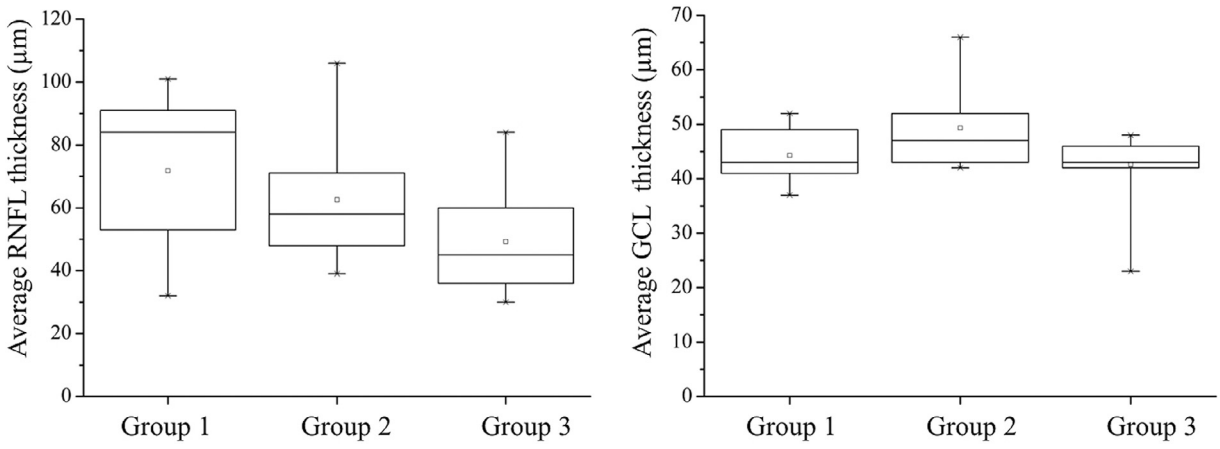
Visual fields. Patients in groups 1 and 2 had a signi□cantly better MD compared with those in group 3 (Table 4 and Figure 2). Insidious Unilateral patients had a signi□cantly worse MD (dB: −12.62 ± 8.31) compared with Insidious Bilateral patients (group 1) ($P = .005$).

OCT parameters. The mean RNFL thickness was higher in group 1 compared with groups 2 and 3, but without achieving statistical signi□cance (Table 4 and Figure 3). The mean GCL thickness was signi□cantly higher in group 2 compared with groups 1 and 3 (Table 4 and Figure 3). There was greater RNFL and GCL thinning for Insidious Unilateral patients (RNFL: 51.50 ± 28.25 μm; GCL: 38.08 ± 8.31 μm) compared with Insidious Bilateral patients (group 1), with the difference being statistically signi□cant for GCL thinning ($P = .003$), but not for RNFL thinning ($P = .117$).

DISCUSSION

The present study presents the combined clinical and genetic data of a large cohort of patients with childhood-onset LHON. We de□ned 2 classi□cation systems based on the presumed age of onset and the pattern of visual loss. Our □ndings indicate that both parameters in□uence the □nal visual outcome, potentially related, at least in part, to their impact on developmental visual maturation and to the plasticity of the visual cortex.

We did not identify any children with subacute visual loss before the age of 3 years, which either re□ects the true course of LHON in this age group or the dif□culties in recognizing visual loss in very young children. For children with disease onset before 3 years of age, group 1 (Insidious Bilateral) and Insidious Unilateral represent about one-third (28.4%) of the entire cohort in this study. LHON should therefore be considered in the differential diagnosis when evaluating children with subnormal vision due to suspected optic atrophy.



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Although insidious onset in LHON has previously been described,[22,24,29] we propose this pattern of visual loss for those with disease onset before 3 years of age. It is not always possible to separate the etiology of visual loss in this age group, which could reflect a combination of the neurodegenerative process directly linked with LHON and abnormal childhood visual development.

In our proposed classification, subclinical involvement refers to a patient who is not subjectively aware of visual loss, but on ophthalmologic examination, there is evidence of mild functional impairment (VA and/or VF) with clear structural evidence of retinal ganglion cell loss on OCT.[18] Although speculative, these cases may denote an abortive onset, which did not progress to the anatomical threshold of retinal ganglion cell loss, which would result in symptomatic visual deterioration.

Unilateral cases of childhood LHON are relatively rare, characterized by severe visual loss usually in association with a strabismus.[32,36] Although strabismus is a relatively common and nonspecific finding in children, almost all unilateral cases had this feature. In families known to have LHON, the occurrence of a strabismus could indicate an underlying unilateral optic neuropathy with visual impairment. The pattern and timing of second eye involvement defined a further subgrouping. The second eye could be involved subclinically or at a later age (≥15 years old). This delay in second eye involvement has been described as rare in adult-onset LHON.[37–40] The specific pattern of Insidious Unilateral onset in early infancy is quite peculiar, and this asymmetric involvement could arise because of subtle anatomical differences between the 2 eyes,[41] such as differences in the architecture and size of the optic nerve head, and the number of axons that are known to vary by up to 20% between eyes.[42,43]

Childhood LHON carries a better visual prognosis compared with disease onset in young adulthood.[22] In our cohort, visual recovery occurred in 64.8% to 83.3% of eyes and a final VA of at least 0.5 was achieved in 40.7% to 51.8% of eyes. In children with subacute visual loss (groups 2 and 3), the visual prognosis worsened with age, with those becoming affected between the ages of 9 and 12 years (group 3) showing more similarity with the classical adult form of LHON.

Group 1, Insidious Bilateral, which includes patients with disease onset <3 years old, seem to have a comparable visual outcome to group 2. In contrast, patients with Insidious Unilateral onset had the worst prognosis, with the lowest mean VA and no eyes achieving VA ≥0.5.

Subclinical cases. The m.14484T>C mutation is therefore associated with a better prognosis in childhood LHON, similar to what has been reported in adult-onset LHON.[9,15] It remains to be proven whether the more frequent occurrence of the m.14484T>C mutation in childhood LHON contributes to the earlier presumed age of onset and/or the better visual outcome. The familial recurrence of childhood LHON cases is intriguing, and this observation points toward the role of secondary genetic modifiers that need to be explored further.

Correlating functional parameters (VA and VF) with structural OCT parameters, patients in group 2 had a better visual prognosis with relative RNFL and GCL preservation. Patients with Insidious Unilateral disease had a worse visual prognosis consistent with the more pronounced RNFL and GCL thinning. Patients in group 3 had the worst visual prognosis with the greatest decrease in RNFL and GCL thickness, similar to what is observed in the adult form of LHON.

In conclusion, children who lose vision from LHON before the age of 9 years have a better visual prognosis compared with those who become affected in later years. This likely represents a *"form frustre"* of the disease accounting for the atypical presentation and natural history of childhood-onset LHON. Strabismus is also frequent among young children who lose vision before 3 years of age. LHON should therefore be considered in children with unexplained subnormal vision and an associated strabismus, with genetic testing requested as part of the investigative workup to avoid diagnostic delays.

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