Childhood-onset Leber hereditary optic neuropathy

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ABSTRACT
Background The onset of Leber hereditary optic neuropathy (LHON) is relatively rare in childhood. This study describes the clinical and molecular genetic features observed in this specific LHON subgroup.

Methods Our retrospective study consisted of a UK paediatric LHON cohort of 27 patients and 69 additional cases identified from a systematic review of the literature. Patients were included if visual loss occurred at the age of 12 years or younger with a confirmed pathogenic mitochondrial DNA mutation: m.3460G>A, m.11778G>A or m.14484T>C.

Results In the UK paediatric LHON cohort, three patterns of visual loss and progression were observed: (1) classical acute (17/27, 63%); (2) slowly progressive (4/27, 15%); and (3) insidious or subclinical (6/27, 22%). Diagnostic delays of 3–15 years occurred in children with an insidious mode of onset. Spontaneous visual recovery was more common in patients carrying the m.3460G>A and m.14484T>C mutations compared with the m.11778G>A mutation. Based a meta-analysis of 67 patients with available visual acuity data, 26 (39%) patients achieved a final best-corrected visual acuity (BCVA) ≥0.5 Snellen decimal in at least one eye, whereas 13 (19%) patients had a final BCVA <0.05 in their better seeing eye.

Conclusions Although childhood-onset LHON carries a relatively better visual prognosis, approximately 1 in 5 patients will remain within the visual acuity criteria for legal blindness in the UK. The clinical presentation can be insidious and LHON should be considered in the differential diagnosis when faced with a child with unexplained subnormal vision and optic disc pallor.

INTRODUCTION
Leber hereditary optic neuropathy (LHON) (OMIM 535000) is a mitochondrial disorder that classically presents with acute or subacute bilateral loss of central vision in young adult men.1-3 About 90% of patients carry one of the three major disease-causing LHON mitochondrial DNA (mtDNA) mutations (MTND1m.3460G>A, MTND4m.11778G>A and MTND6m.14484T>C), all of which encode for critical complex I subunits of the mitochondrial respiratory chain.4 The greater availability of molecular genetic testing has broadened the phenotypical spectrum associated with LHON to include patients with more slowly progressive visual deterioration exceeding 6 months in duration, and those with an insidious/subclinical course characterised by the incidental discovery of subnormal vision and optic atrophy in the absence of overt visual symptoms.5,5 Although disease conversion can occur anywhere from the first to the eight decade of life, the peak age of onset of visual loss among LHON carriers is 20–30 years old.1,4 Childhood-onset disease is relatively rare and less than 10% of patients were 12 years old or younger at the time of diagnosis in previously published case series.1,6-10 Although there are limited data on this important patient subgroup, the phenotype seems distinct from classical adult-onset LHON with atypical patterns of vision loss and a better visual prognosis as reported in a previously published study of 18 patients with childhood-onset LHON.7

The aim of our study was to describe the clinical and molecular genetic characteristics associated with childhood-onset LHON, in particular the disease course and visual prognosis to better inform genetic counselling. We retrieved data for all eligible patients with LHON that were seen at three major diagnostic centres for inherited optic neuropathies in the UK. This UK paediatric LHON cohort was then combined with additional cases identified from a systematic review of the literature to generate a comprehensive meta-analysis of childhood LHON.

PATIENTS AND METHODS
Study population
This is a retrospective observational study approved by the local ethics committee at Moorfields Eye Hospital and it conformed to the standards set by the Declaration of Helsinki. Patients with LHON with disease onset at the age of 12 years or younger were identified from the clinical and genetic databases of the three main national diagnostic centres for inherited optic neuropathies in the UK (London, Oxford and Newcastle upon Tyne). We only included patients who carried one of the three canonical pathogenic mtDNA mutations, that is, m.3460G>A, m.11778G>A and m.14484T>C. Additional clinical information where relevant was sought from the original referring clinicians.

Best-corrected visual acuities (BCVAs) at disease onset, at the nadir and at the last follow-up clinic visit were recorded. Patients were subclassified into three groups based on the mode of onset and progression of vision loss: (1) acute, if visual acuity deteriorated rapidly reaching the nadir within 6 months from disease onset; (2) slowly progressive, if visual deterioration occurred over a period exceeding 6 months; and (3) insidious or subclinical, if the patient was clinically asymptomatic at the time that a diagnosis of optic atrophy or subnormal vision was made, and there was no change in visual acuity during subsequent follow-ups.5,5 Spontaneous visual recovery was defined as an improvement of BCVA by two lines or more on the ETDRS chart or from off-chart to on-chart visual acuity (0.05
Snellen decimal (SD)). A binocular visual acuity of at least 0.5 (6/12) is the minimum standard for driving in the UK (https://www.gov.uk/driving-eyesight-rules, accessed on 8 November 2016) and below 0.05 (3/60) is the legal definition of registrable blindness in the UK (https://www.gov.uk/government/publications/guidance-published-on-registering-a-vision-impairment-as-a-disability, accessed on 8 November 2016).

When available, spectral-domain optical coherence tomography (SD-OCT) data were retrieved from the database of the Spectralis (Heidelberg Engineering, Heidelberg, Germany) and Cirrus HD-OCT 4000 (Carl Zeiss Meditec, Dublin, California, USA) platforms, and compared with the normative data described elsewhere.\textsuperscript{11,12}

**Systematic literature review**

A comprehensive literature search was conducted using the search terms ‘LHON’, ‘Leber hereditary optic neuropathy’ or ‘Leber’s hereditary optic neuropathy’ and ‘child’, ‘childhood’, ‘paediatric’ or ‘paediatric’ on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/, accessed on 8 November 2016). We also reviewed all the papers that included previously published publications on childhood LHON in their reference lists. A patient with LHON was included in our meta-analysis only if there was confirmation of the m.3460G>A, m.11778G>A or m.14484T>C mtDNA mutation, and disease onset was clearly stated as being before the age of 12 years or younger. None of the patients included in the historical case series was present in the UK paediatric LHON cohort. Due to the retrospective nature of our systematic literature review, more detailed clinical information regarding visual acuity and disease progression was not available for 29 of the 69 eligible patients included in our historical case series.

**Statistical analysis**

The Kruskal-Wallis test and Mann-Whitney U independent samples test were used for comparing the age at onset between the LHON genotypes and the distribution of retinal layer thickness in LHON and control eyes, respectively. The Spearman’s rank correlation test was used to assess for the strength of dependence between BCVA and retinal layer thickness (IBM Statistical Package of Social Sciences (SPSS) 22 V.100).

**RESULTS**

**UK paediatric LHON cohort**

The UK paediatric LHON cohort included 27 patients who were 2–11 years old (mean=6.9 years, SD=2.9 years) at the time of onset of visual loss or when subnormal visual acuity or optic disc pallor first became apparent (table 1). Thirteen patients (48%) carried the m.11778G>A mutation, seven patients (26%) the m.3460G>A mutation and seven patients (26%) the m.14484T>C mutation (table 2). Patients 24–27 belonged to the same family and out of five affected family members, four of them developed visual loss before the age of 6 years. There was a known family history of LHON in 19 probands (70%). The male:female ratio varied between 2.5 and 3.3 for the three primary LHON mtDNA mutations with an overall male:female ratio of 3.0. There was no statistically significant difference in the age of disease onset between the LHON genotypes (Kruskal-Wallis test, p=0.831).

The majority of patients (17/27, 63%) experienced acute or subacute visual loss with the nadir being reached within 6 months of first disease onset. This mode of presentation was the most common in children harbouring the m.3460G>A mutation (6/7, 86%). In four patients (15%), visual acuity deteriorated slowly over a period extending up to 2 years. Three patients in this subgroup carried the m.14484T>C mutation and one the m.11778G>A mutation. There was an unexpectedly large number of children (6/27, 22%) with insidious or subclinical vision loss in the UK paediatric LHON cohort. Subnormal vision or optic disc pallor were detected during the first 2 years of life (n=4) or after failing the preschool visual screening assessment (n=2), which is mandatory in the UK for all 4–5-year-olds (table 1). None of these children demonstrated or were suspected of having impaired visual performance during their early years and no visual deterioration occurred on subsequent follow-up. Molecular genetic confirmation of LHON in this insidious/subclinical group was markedly delayed between 3 years and 15 years due to the atypical presentation.

The mean final BCVA in the whole group of patients with childhood-onset LHON was 0.39 SD (SD=0.38, range=light perception—1.2 SD, median=0.25) with a mean disease duration of 18 years (SD=16 years, range=1–56 years, median=16 years). BCVA was ≥0.5 in 20/54 (37%) eyes and 14/27 (52%) patients had at least 1 eye with BCVA ≥0.5. Conversely, BCVA was <0.05 in 11/54 (20%) eyes and 5/27 (19%) patients met the legal definition of blindness with a BCVA<0.05 in their better seeing eye. The m.11778G>A mutation was associated with a worse visual outcome compared with the m.3460G>A and m.14484T>C mutations (table 2 and figure 1). Ten (37%) patients had asymmetrical final BCVA with a difference ≥2 lines on the ETDRS chart, and this was associated with: (1) asymmetrical visual loss in the acute stage (n=2); (2) asymmetrical visual recovery following an acute disease onset (n=2); (3) slowly progressive visual loss (n=3); and (4) an insidious/subclinical course (n=3). Patient 26, who harboured the m.14484T>C mutation, presented with slowly progressive visual deterioration in only one eye. In patients presenting with acute LHON, spontaneous visual recovery occurred in 20/34 (59%) eyes and 16 (80%) of the recovered eyes achieved a BCVA ≥0.5. The mean time to recovery was 29 months (SD=18 months, range=9–60 months) and there were no significant differences between mutation subgroups (m.3460G>A, mean=28 months; m.11778G>A, mean=27 months; m.14484T>C, mean=32 months; Kruskal-Wallis test, p=0.958). Visual outcome was bimodal in the acute LHON group with a BCVA ≥0.5 in 17/34 (50%) eyes and <0.05 in 10/34 (29%) eyes (figure 2). The majority of eyes for patients classified as having slowly progressive (5/8, 63%) or insidious/subclinical (11/12, 82%) LHON had BCVA <0.5.

SD-OCT imaging of the optic nerve head was available for 26 eyes of 13 patients. There was a significant reduction in the average peripapillary retinal nerve fibre layer (RNFL) thickness ranging from 49.0% to 58.4% compared with control values. On subgroup analysis, there was no significant correlation between BCVA and peripapillary RNFL thickness in any of the individual quadrants (data not shown). Perifoveal volumetric retinal SD-OCT scans were available for 10 eyes of five patients. Retinal thickness was significantly reduced in the LHON group (mean ±SD=295.5±17.7 μm) compared with normal controls (mean ±SD=340.8±13.3 μm, Mann-Whitney U test, p<0.001). This was specifically due to marked thinning of the ganglion cell layer-inner plexiform layer (GCL-IPL) complex in the LHON group (mean ±SD=43.2±2.9 μm) compared with normal controls (mean ±SD=93.5±7.8 μm, Mann-Whitney U test, p<0.001). There was a statistically significant correlation between BCVA and the remaining GCL-IPL thickness (Spearman’s r=−0.773, p=0.009, online supplementary figure S1).

**Meta-analysis of childhood-onset LHON**

Our systematic review of the literature identified 69 patients with LHON with onset of vision loss at the age of 12 years or
younger (mean=8.5 years, median=8.0 years, range=3–12 years) from 20 original publications covering diverse populations: Australia, Brazil, Chile, China, Finland, France, Germany, Italy, Saudi Arabia, Switzerland, the UK and USA (see online supplementary table S1 and online supplementary appendix). The m.11778G>A mutation accounted for 47/69 (69%) of all the included cases. Visual acuity data were available for 40 patients and overall, 18/79 (23%) eyes achieved a BCVA ≥0.5 whereas 18/79 (23%) eyes achieved a BCVA <0.05. We merged the UK paediatric and historical LHON cohorts to generate a meta-analysis of childhood-onset LHON (see online supplementary table S2 and figure S2). The number of patients

<table>
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<th>Table 1</th>
<th>Demographics and clinical features of patients included in the UK paediatric LHON cohort</th>
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*BCVA recorded at last follow-up clinic visit in Snellen decimal.
†From the same pedigree.
A, acute; BCVA, best corrected visual acuity; BE, both eyes; CF, counting fingers at 0.25 metre; f, female; HM, hand movement; i, insidious; LE, left eye; LP, light perception; m, male; RE, right eye; S, slowly progressive.

<table>
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<th>Table 2</th>
<th>Data summary of patients included in the UK paediatric LHON cohort</th>
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*Number of eyes with visual recovery.
†Number of eyes with BCVA ≥0.5 or <0.05 in Snellen decimal.
BCVA, best corrected visual acuity; f, female; LHON, Leber hereditary optic neuropathy; m, male.
with a BCVA ≥0.5 in at least one eye was 26/67 (39%) whereas
the number of patients with a BCVA <0.05 in their better
seeing eye was 13/67 (19%).

DISCUSSION

LHON is a disease of young adults and due to its relative rarity,
there are limited data on the clinical features and visual pro-
gnosis of childhood LHON. In this study, we first identified a UK
paediatric LHON cohort consisting of 27 patients diagnosed
before the age of 12 years, which was then combined with a
historical cohort of 69 eligible patients from 20 previously pub-
lished reports (see online supplementary appendix). These two
cohorts had similar clinical and molecular genetic profiles and
we therefore combined the data to generate a meta-analysis for
a more comprehensive comparison with classical adult-onset
LHON.

The distribution of the three major disease-causing LHON
mutations (m.3460G>A=19%, m.11778G>A=62.5% and
m.14484T>C=19%) in the childhood cohort is comparable
with previously reported adult LHON case series with the
m.11778G>A mtDNA mutation being the most common geno-
type. As expected, there was a male preponderance, but the
overall male:female ratio of 1.8 is less marked than the fourfold
to fivefold increased risk of visual loss seen among adult male
carriers. The mechanisms contributing to this rather intri-
guing male bias are not fully understood and a number of sec-
condary genetic, hormonal and environmental risk factors
have been implicated. Smoking and to a lesser extent heavy drink-
ing are regarded as important environmental triggers, but these
factors are unlikely to be aetiologically important in young chil-
dren. Although this hypothesis needs to be formally verified, the
less pronounced sex bias in childhood LHON could arise
because it is more heavily genetically determined by nuclear
modifiers, which contribute to an earlier age of onset, but that
are less sex determined or influenced. The other phenotypical
extreme would be late-onset adult cases over the age of 50 years
where environmental risk factors, in particular smoking, are
thought to play a more prominent role in precipitating disease
conversion. A systematic genomic comparison of childhood
LHON, classical acute cases in young adults and late-onset
LHON could therefore prove the key to dissecting the complex
genetic-environmental modulators that contribute to visual loss
in different groups of susceptible carriers.

The classical acute pattern of vision loss was the most
common presentation in childhood LHON, but over a third of
patients either had a slowly progressive onset or even more
strikingly, a subclinical or insidious disease evolution. In a pre-
vious report of 14 children with LHON from Barboni and colleagues,
the 6 patients classified as having a slowly progressive course
achieved better final visual acuities compared with the acute
group. In contrast with this finding, the four patients in
the UK paediatric LHON cohort did not have a better pro-
gnosis, with the vision deteriorating in the majority of eyes to less
than the driving standards, that is, BCVA <0.5. The insidious/
subclinical LHON subgroup was observed with all three major
disease-causing mtDNA mutations and the defining observation
was the significant delays in reaching a confirmed molecular
diagnosis, which ranged from 3 years to 15 years. Visually
asymptomatic children in whom subnormal vision and optic
atrophy, which can be subtle, are detected incidentally have
been reported previously and the diagnostic challenges are likely
to be multifactorial. Visual performance in this age group is
not always impaired due to the inherent adaptive capacity of
young children and importantly, they may not be able to com-
municate changes in their vision effectively to their parents or
guardians. A lack of clinical awareness of LHON in young chil-
dren is also likely to be relevant in explaining the diagnostic
delays in this patient group.

LHON has a major impact on quality of life and the majority
of patients will remain within the criteria for legal blindness. The
observed overall rates of spontaneous visual recovery of
37% for all eyes in the entire UK paediatric LHON cohort and
of 59% for the eyes of patients with acute LHON, are in line
with the corresponding values of 28% and 63% reported by
Barboni and colleagues. Patients with adult-onset LHON hav-
ouring the m.14484T>C mutation have the best visual prog-
nosis with a partial visual recovery rate of 37%–58% compared
with 4%–25% for the m.11778G>A mutation and 22%–25% for
the m.3460G>A mutation. The variations in the reported rates of spontaneous visual recovery reflect possible
sampling bias depending on the cohort size and the different
criteria used to define a visually significant change in visual
acuity from the nadir. In our study, the rates of spontaneous
visual recovery were 57%, 23% and 43% for the m.3460G>A,
m.11778G>A and m.14484T>C mutations, respectively.
Children carrying the m.3460G>A mutation therefore seem to
have a better visual prognosis, and the recovery rate observed

Figure 1  Distribution of best-corrected visual acuity (BCVA) in the UK
paediatric Leber hereditary optic neuropathy (LHON) cohort stratified
according to the genotype. Off-chart refers to the number of eyes with
BCVA worse than 0.05.

Figure 2  Distribution of best-corrected visual acuity (BCVA) in the UK
paediatric Leber hereditary optic neuropathy (LHON) cohort stratified
according to the pattern of visual loss at disease onset. Off-chart refers
to the number of eyes with BCVA worse than 0.05.
with the m.11778G>A mutation is also higher, compared with the clinical impression in patients with adult-onset LHON.2 3

Based on our meta-analysis of 67 patients for whom visual acuity data were available, 39% of patients achieved a BCVA ≥0.5 in at least one eye whereas 19% of patients had a BCVA <0.05 in their better seeing eye. A more favourable final visual outcome was observed for all three genotypes in our childhood-onset LHON cohort compared with previously published figures (m.3460G>A: 14% vs 55–96%; m.11778G>A: 45% vs 73–98%; and m.14484T>C mutation: 6% vs 30–50% of eyes achieving a BCVA <0.1).1 9 20 21 Mitochondrial turn-over is implicated in the pathogenesis of LHON, both mitochondrial biogenesis and mitophagy being increased in fibroblasts of patients with LHON.21 24 The known age-related decline in mitophagy, and hence presumably mitochondrial biogenesis, may underlie this difference from adult disease.25

In conclusion, childhood-onset LHON represents a distinct phenotypic subgroup characterised by a more varied clinical evolution and a more favourable visual prognosis compared with classical adult LHON. Importantly, children do not always develop acute or subacute visual symptoms and a high index of suspicion is required in children presenting with unexplained subnormal vision and optic disc pallor to avoid potentially long diagnostic delays.

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Correction notice This article has been corrected since it was published Online First. Affiliation number 9 has been added to author Patrick Yu-Wai-Man.

Contributors Research design: AM, MV, ATM, PY-W-M. Data acquisition and/or research execution: AM, RB, JP, RIA, MAR, MM, ARW, MV, ATM, PY-W-M. Data analysis and/or interpretation: AM, PFC, MV, ATM, PY-W-M. Manuscript preparation: AM, PY-W-M.

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Competing interests PY-W-M holds a consultancy agreement with GenSight Biologics (Paris, France).

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