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Childhood-Onset Leber Hereditary Optic Neuropathy

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Data analysis and/or interpretation: AM, PFC, MV, ATM, PYWM

Manuscript preparation: AM, PYWM

Disclosures

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Keywords: Childhood; Leber hereditary optic neuropathy (LHON); mitochondrial disease; visual prognosis; optic atrophy.

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 old 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, 3 patterns of visual loss and progression were observed: (i) classical acute (17/27, 63%); (ii) slowly progressive (4/27, 15%); and (iii) 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.

Conclusion:

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.

Word count: 250

Synopsis

Childhood-onset Leber hereditary optic neuropathy (LHON) carries a relatively better visual prognosis. Patients can present atypically with an insidious/subclinical course and LHON should be considered in children with unexplained subnormal vision and optic disc pallor.

Word count: 35

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 (*MTND1* m.3460G>A, *MTND4* m.11778G>A and *MTND6* m.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 phenotypic 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.[1, 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 is 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 LHON patients that were seen at three major diagnostic centres for inherited optic neuropathies in the United Kingdom (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.

117 ## Patients and Methods

118 ### Study Population

119 This is a retrospective observational study approved by the local ethics committee at Moorfields Eye
120 Hospital and it conformed to the standards set by the Declaration of Helsinki. LHON patients with
121 disease onset at the age of 12 years old or younger were identified from the clinical and genetic data
122 bases of the three main national diagnostic centres for inherited optic neuropathies in the UK
123 (London, Oxford and Newcastle upon Tyne). We only included patients who carried one of the three
124 canonical pathogenic mtDNA mutations, i.e., m.3460G>Am m.11778G>A and m.14484T>C.
125 Additional clinical information where relevant were sought from the original referring clinicians. Best
126 corrected visual acuity (BCVA) at disease onset, at the nadir and at the last follow-up clinic visit were
127 recorded. Patients were sub-classified into three groups based on the mode of onset and
128 progression of visual loss: (i) *acute*, if visual acuity deteriorated rapidly reaching the nadir within 6
129 months from disease onset; (ii) *slowly progressive*, if visual deterioration occurred over a period
130 exceeding 6 months; and (iii) *insidious* or *subclinical*, if the patient was clinically asymptomatic at the
131 time that a diagnosis of optic atrophy or subnormal vision was made, and there was no change in
132 visual acuity during subsequent follow-ups.[1, 7] Spontaneous visual recovery was defined as an
133 improvement of BCVA by two lines or more on the Early Treatment Diabetic Retinopathy Study
134 (ETDRS) chart or from off-chart to on-chart visual acuity (0.05 Snellen decimal). A binocular visual
135 acuity of at least 0.5 (6/12) is the minimum standard for driving in the UK
136 (https://www.gov.uk/driving-eyesight-rules, accessed on 8 November 2016) and below 0.05 (3/60) is
137 the legal definition of registrable blindness in the UK
138 (https://www.gov.uk/government/publications/guidance-published-on-registering-a-vision-
139 impairment-as-a-disability, accessed on 8 November 2016).
140 When available, spectral-domain optical coherence tomography (SD-OCT) data was retrieved
141 from the database of the Spectralis™ (Heidelberg Engineering Ltd., Heidelberg, Germany) and Cirrus

142 HD-OCT 4000™ (Carl Zeiss Meditec, Inc., Dublin, CA, USA) platforms, and compared with the
143 normative data described elsewhere.[11, 12]
144
145 **Systematic Literature Review**
146 A comprehensive literature search was conducted using the search terms "LHON", "Leber hereditary
147 optic neuropathy"or "Leber's hereditary optic neuropathy" and "child", "childhood", "paediatric"
148 or "paediatric" on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/, accessed on 8 November
149 2016). We also reviewed all the papers that included previously published publications on childhood
150 LHON in their reference lists. A LHON patient was included in our meta-analysis only if there was
151 confirmation of the m.3460G>A, m.11778G>A, or m.14484T>C mtDNA mutation, and disease onset
152 was clearly stated as being before the age of 12 years old or younger. None of the patients included
153 in the historical case series was present in the UK paediatric LHON cohort. Due to the retrospective
154 nature of our systematic literature review, more detailed clinical information regarding visual acuity
155 and disease progression was not available for 29 of the 69 eligible patients included in our historical
156 case series.
157
158 **Statistical Analysis**
159
160 The Kruskal-Wallis test and Mann-Whitney *U* independent samples test were used for comparing the
161 age at onset between the LHON genotypes and the distribution of retinal layer thickness in LHON
162 and control eyes, respectively. The Spearman's rank correlation test was used to assess for the
163 strength of dependence between BCVA and retinal layer thickness (IBM Statistical Package of Social
164 Sciences (SPSS) 22 v100).
165
166 **Results**

167 **UK Paediatric LHON Cohort**

168 The UK paediatric LHON cohort included 27 patients who were 2 to 11 years old (mean = 6.9 years,
169 standard deviation (SD) = 2.9 years) at the time of onset of visual loss or when subnormal visual
170 acuity or optic disc pallor first became apparent (**Table 1**). Thirteen patients (48%) carried the
171 m.11778G>A mutation, 7 patients (26%) the m.3460G>A mutation, and 7 patients (26%) the
172 m.14484T>C mutation (**Table 2**). Patients 24-27 belonged to the same family and out of 5 affected
173 family members, 4 of them developed visual loss before the age of 6 years old. There was a known
174 family history of LHON in 19 probands (70%). The male:female ratio varied between 2.5 to 3.3 for
175 the 3 primary LHON mtDNA mutations with an overall male:female ratio of 3.0. There was no
176 statistically significant difference in the age of disease onset between the LHON genotypes (Kruskal-
177 Wallis test, p=0.831).

178 The majority of patients (17/27, 63%) experienced acute or subacute visual loss with the
179 nadir being reached within 6 months of first disease onset. This mode of presentation was the most
180 common in children harbouring the m.3460G>A mutation (6/7, 86%). In 4 patients (15%), visual
181 acuity deteriorated slowly over a period extending up to 2 years. Three patients in this subgroup
182 carried the m.14484T>C mutation and one the m.11778G>A mutation. There was an unexpectedly
183 large number of children (6/27, 22%) with insidious or subclinical vision loss in the UK paediatric
184 LHON cohort. Subnormal vision or optic disc pallor were detected during the first 2 years of life (n=4)
185 or after failing the preschool visual screening assessment (n=2), which is mandatory in the UK for all
186 4-5 year olds (**Table 1**). None of these children demonstrated or were suspected of having impaired
187 visual performance during their early years and no visual deterioration occurred on subsequent
188 follow-up. Molecular genetic confirmation of LHON in this insidious/subclinical group was markedly
189 delayed between 3 to 15 years due to the atypical presentation.

190 The mean final BCVA in the whole group of patients with childhood-onset LHON was 0.39
191 Snellen decimal (SD = 0.38, range = light perception – 1.2 Snellen decimal, median = 0.25) with a

192 mean disease duration of 18 years (SD = 16 years, range = 1 - 56 years, median = 16 years). BCVA
193 was ≥ 0.5 in 20/54 (37%) eyes and 14/27 (52%) patients had at least one eye with BCVA ≥ 0.5.
194 Conversely, BCVA was < 0.05 in 11/54 (20%) eyes and 5/27 (19%) patients met the legal definition of
195 blindness with a BCVA < 0.05 in their better seeing eye. The m.11778G>A mutation was associated
196 with a worse visual outcome compared with the m.3460G>A and m.14484T>C mutations (**Table 2**,
197 **Figure 1**). Ten (37%) patients had asymmetric final BCVA with a difference ≥ 2 lines on the ETDRS
198 chart, and this was associated with: (i) asymmetric visual loss in the acute stage (n = 2); (ii)
199 asymmetric visual recovery following an acute disease onset (n = 2); (iii) slowly progressive visual
200 loss (n = 3); and (iv) an insidious/subclinical course (n = 3). Patient 26, who harboured the
201 m.14484T>C mutation, presented with slowly progressive visual deterioration in only one eye. In
202 patients presenting with acute LHON, spontaneous visual recovery occurred in 20/34 (59%) eyes and
203 16 (80%) of the recovered eyes achieved a BCVA ≥ 0.5. The mean time to recovery was 29 months
204 (SD = 18 months, range = 9 – 60 months) and there was no significant differences between mutation
205 subgroups (m.3460G>A, mean = 28 months; m.11778G>A, mean = 27 months; m.14484T>C, mean =
206 32 months; Kruskal-Wallis test, p=0.958). Visual outcome was bimodal in the acute LHON group with
207 a BCVA ≥ 0.5 in 17/34 (50%) eyes and < 0.05 in 10/34 (29%) eyes (**Figure 2**). The majority of eyes for
208 patients classified as having slowly progressive (5/8, 63%) or insidious/subclinical (11/12, 82%) LHON
209 had BCVA < 0.5.

210 SD-OCT imaging of the optic nerve head was available for 26 eyes of 13 patients. There was a
211 significant reduction in the average peripapillary retinal nerve fibre layer (RNFL) thickness ranging
212 from 49.0% to 58.4% compared with control values. On subgroup analysis, there was no significant
213 correlation between BCVA and peripapillary RNFL thickness in any of the individual quadrants (data
214 not shown). Perifoveal volumetric retinal SD-OCT scans were available for 10 eyes of 5 patients.
215 Retinal thickness was significantly reduced in the LHON group (mean ± SD = 295.5 ± 17.7 μm)
216 compared with normal controls (mean ± SD = 340.8 ± 13.3 μm, Mann-Whitney *U* test p < 0.001). This
217 was specifically due to marked thinning of the GCL-IPL complex in the LHON group (mean ± SD = 43.2

218 ± 2.9 μm) compared with normal controls (mean ± SD = 93.5 ± 7.8 μm, Mann-Whitney *U* test p <
219 0.001). There was a statistically significant correlation between BCVA and the remaining ganglion cell
220 layer-inner plexiform layer (GCL-IPL) thickness (Spearman *rho*=-0.773, p=0.009, **Supplementary**
221 **Figure 1**).

222

223 **Meta-Analysis of Childhood-Onset LHON**

224 Our systematic review of the literature identified 69 LHON patients with onset of vision loss at the
225 age of 12 years old or younger (mean = 8.5 years, median = 8.0 years, range = 3 - 12 years) from 20
226 original publications covering diverse populations: Australia, Brazil, Chile, China, Finland, France,
227 Germany, Italy, Saudi Arabia, Switzerland, the UK, and the USA (**Supplementary Table**
228 **1**).[Supplementary appendix] The m.11778G>A mutation accounted for 47/69 (69%) of all the
229 included cases. Visual acuity data was available for 40 patients and overall, 18/79 (23%) eyes
230 achieved a BCVA ≥ 0.5 whereas 18/79 (23%) eyes achieved a BCVA < 0.05. We merged the UK
231 paediatric and historical LHON cohorts to generate a meta-analysis of childhood-onset LHON
232 (**Supplementary Table 2**, **Supplementary Figure 2**). The number of patients with a BCVA ≥ 0.5 in at
233 least one eye was 26/67 (39%) whereas the number of patients with a BCVA < 0.05 in their better
234 seeing eye was 13/67 (19%).

235

236 **Discussion**

237 LHON is a disease of young adults and due to its relative rarity, there is limited data on the clinical
238 features and visual prognosis of childhood LHON. In this study, we first identified a UK paediatric
239 LHON cohort consisting of 27 patients diagnosed before the age of 12 years old, which was then
240 combined with a historical cohort of 69 eligible patients from 20 previously published reports

241 (**Supplementary Appendix**). These two cohorts had similar clinical and molecular genetics profile
242 and we therefore combined the data to generate a meta-analysis for a more comprehensive
243 comparison with classical adult-onset LHON.

244 The distribution of the three major disease causing LHON mutations (m.3460G>A = 19%,
245 m.11778G>A = 62.5%, and m.14484T>C = 19%) in the childhood cohort is comparable with
246 previously reported adult LHON case series with the m.11778G>A mtDNA mutation being the most
247 common genotype. As expected, there was a male preponderance, but the overall male:female ratio
248 of 1.8 is less marked than the 4-5 fold increased risk of visual loss seen among adult male
249 carriers.[13-14] The mechanisms contributing to this rather intriguing male bias are not fully
250 understood and a number of secondary genetic, hormonal and environmental risk factors have been
251 implicated.[15] Smoking and to a lesser extent heavy drinking are regarded as important
252 environmental triggers, but these factors are unlikely to be aetiologically important in young
253 children. Although this hypothesis needs to be formally verified, the less pronounced sex bias in
254 childhood LHON could arise because it is more heavily genetically determined by nuclear modifiers,
255 which contribute to an earlier age of onset, but that are less sex determined or influenced. The other
256 phenotypic extreme would be late-onset adult cases over the age of 50 years old where
257 environmental risk factors, in particular smoking, are thought to play a more prominent role in
258 precipitating disease conversion.[16-17] A systematic genomic comparison of childhood LHON,
259 classical acute cases in young adults and late-onset LHON could therefore prove the key to dissecting
260 the complex genetic-environmental modulators that contribute to visual loss in different groups of
261 susceptible carriers.

262 The classical acute pattern of vision loss was the most common presentation in childhood
263 LHON, but over one third of patients either had a slowly progressive onset or even more strikingly, a
264 subclinical or insidious disease evolution. In a previous report of 14 children with LHON from *Barboni*
265 *and colleagues*, the 6 patients classified as having a slowly progressive course achieved better final

266 visual acuities compared with the acute group.[7] In contrast with this finding, the 4 patients in the
267 UK paediatric LHON cohort did not have a better prognosis, with the vision deteriorating in the
268 majority of eyes to less than the driving standards, i.e., BCVA < 0.5. The insidious/subclinical LHON
269 subgroup was observed with all 3 major disease causing mtDNA mutations and the defining
270 observation was the significant delays in reaching a confirmed molecular diagnosis, which ranged
271 from 3 to 15 years. Visually asymptomatic children in whom subnormal vision and optic atrophy,
272 which can be subtle, are detected incidentally have been reported previously and the diagnostic
273 challenges are likely to be multifactorial.[10, 18] Visual performance in this age group is not always
274 impaired due to the inherent adaptive capacity of young children and importantly, they may not be
275 able to communicate changes in their vision effectively to their parents or guardians. A lack of
276 clinical awareness of LHON in young children is also likely to be relevant in explaining the diagnostic
277 delays in this patient group.

278 LHON has a major impact on quality of life and the majority of patients will remain within
279 the criteria for legally blindness.[19]The observed overall rates of spontaneous visual recovery of
280 37% for all eyes in the entire UK paediatric LHON cohort and of 59% for the eyes of patients with
281 acute LHON, are in line with the corresponding values of 28% and 63% reported by *Barboni and*
282 *colleagues*.[7] Adult-onset LHON patients harbouring the m.14484T>C mutation have the best visual
283 prognosis with a partial visual recovery rate of 37-58% compared with 4-25% for the m.11778G>A
284 mutation, and 22-25% for the m.3460G>A mutation.[6, 8, 20-22] The variations in the reported rates
285 of spontaneous visual recovery reflect possible sampling bias depending on the cohort size and the
286 different criteria used to define a visually significant change in visual acuity from the nadir.[3] In our
287 study, the rates of spontaneous visual recovery were 57%, 23% and 43% for the m.3460G>A,
288 m.11778G>A and m.14484T>C mutations, respectively. Children carrying the m.3460G>A mutation
289 therefore seem to have a better visual prognosis, and the recovery rate observed with the
290 m.11778G>A mutation is also higher, compared with the clinical impression in patients with adult-
291 onset LHON.[6, 21] Based on our meta-analysis of 67 patients for whom visual acuity data was

292 available, 39% of patients achieved a BCVA ≥ 0.5 in at least one eye whereas 19% of patients had a
293 BCVA < 0.05 in their better seeing eye. A more favourable final visual outcome was observed for all
294 three genotypes in our childhood-onset LHON cohort compared with previously published figures
295 (m.3460G>A: 14% versus 55-96%; m.11778G>A: 45% versus 73-98%; and m.14484T>C mutation: 6%
296 versus 30-50% of eyes achieving a BCVA < 0.1).[1, 6, 8, 20-21] Mitochondrial turnover is implicated in
297 the pathogenesis of LHON, both mitochondrial biogenesis and mitophagy being increased in
298 fibroblasts of LHON patients.[23-24] The known age-related decline in mitophagy, and hence
299 presumably mitochondrial biogenesis, may underlie this difference from adult disease.[25]
300 In conclusion, childhood-onset LHON represents a distinct phenotypic subgroup
301 characterised by a more varied clinical evolution and a more favourable visual prognosis compared
302 with classical adult LHON. Importantly, children do not always develop acute or subacute visual
303 symptoms and a high index of suspicion is required in children presenting with unexplained
304 subnormal vision and optic disc pallor to avoid potentially long diagnostic delays.
305
306

307

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Table 1. Demographics and clinical features of patients included in the UK paediatric LHON cohort.

Patient	Mutation	Family history	f/m	Age at onset (y)	Mode of onset	Disease progression	Final BCVA[ψ]		Time from onset (y)
							RE	LE	
1	11778	yes	f	6	S	Gradual visual deterioration over 2 years.	0.17	0.02	47
2	11778	yes	f	8	A	No recovery	LP	LP	56
3	11778	yes	f	9	A	No recovery	0.03	0.03	38
4	11778	yes	m	11	A	Worst BCVA: HM BE. Recovery within 12 months from onset.	0.76	0.50	1
5	11778	no	m	8	A	No recovery	CF	CF	33
6	11778	no	m	3	I	Subnormal vision since birth.	0.17	0.50	52
7	11778	no	m	9	A	Worst BCVA: 0.08 RE, 0.4 LE. Asymmetric.	0.10	0.50	18
8	11778	yes	m	11	A	No recovery	0.07	0.10	2
9	11778	no	m	2	I	Subnormal vision detected when 2 years old. LHON diagnosed at the age of 8 yrs.	0.25	0.08	17
10	11778	yes	m	8	A	No recovery	CF	CF	10
11	11778	no	m	10	A	Worst BCVA: CF BE. Recovery within 24 months from onset. Asymmetric recovery.	0.08	0.66	7
12	11778	yes	m	2	I	Subnormal vision detected when 2 years old. LHON diagnosed at the age of 6 yrs with BCVA of 0.18 RE and 0.17 LE. Slow visual recovery until 10 yrs old.	0.35	0.36	4
13	11778	yes	m	2	I	Optic atrophy noted at the age of 2 years. LHON diagnosed at the age of 17 years.	0.40	0.10	15
14	3460	yes	f	7	A	Worst BCVA: 0.05 BE. Recovery within 4 yrs from onset.	0.79	0.79	4.5

15	3460	no	f	11	A	No recovery.	CF	CF	10
16	3460	yes	m	4	I	Poor visual acuity noticed at pre-school screening assessment.	0.17	0.17	16
17	3460	no	m	6	A	Asymmetric visual recovery.	0.67	0.25	18
18	3460	yes	m	8	A	Worst BCVA: 0.05 BE. Recovery within 12 months from onset.	1.20	1.20	1
19	3460	yes	m	10	A	Worst BCVA: HM RE, CF LE. Recovery	0.33	0.50	1.5
20	3460	no	m	5	A	Worst BCVA: 0.1 BE. Recovery within 24 months from onset.	1.00	1.00	2
21	14484	yes	f	9	S	Gradual visual deterioration over 2 years.	0.17	0.25	29
22	14484	yes	m	10	A	Recovery within 9 months from onset.	1.00	1.00	16
23	14484	yes	m	5	I	Poor visual acuity noticed at pre-school screening assessment.	0.25	0.25	39
24*	14484	yes	f	6	A	Worst BCVA: 0.02 RE, 0.2 LE. Recovery within 5 yrs from onset.	0.91	1.00	18
25*	14484	yes	m	6	S	Asymmetric visual recovery.	0.69	0.14	13
26*	14484	yes	m	4	S	Slowly progressive visual deterioration in the left eye only.	1.00	0.10	13
27*	14484	yes	m	5	A	Off-chart vision (BE) at the nadir. Asymmetric recovery within 2-3 yrs from onset.	0.07	0.67	28

* From the same pedigree. ψ Best-corrected visual acuity (BCVA) recorded at last follow-up clinic visit in Snellen decimal.
Abbreviations: 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; m, male; RE, right eye; S, slowly progressive.

Table 2. Data summary of patients included in the UK paediatric LHON cohort.

Mutation	Patients (pedigrees)	Sex			Age at onset (y)	Acute onset	Slowly progressive onset	Insidious / subclinical onset	Visual recovery *	BCVA	BCVA# ≥ 0.5	BCVA# <0.05
	n	f	m	m:f	Mean Median	n (%)	n (%)	n (%)	n (%)	Mean Median	n (%)	n (%)
11778	13 (13)	3	10	3.3	6.8 8.0	8 (61)	1 (7)	4 (30)	6 (23)	0.20 0.10	5/26 (19)	9/26 (35)
3460	7 (7)	2	5	2.5	7.3 7.0	6 (86)	0	1 (14)	8 (57)	0.60 0.73	8/14 (57)	2/14 (14)
14484	7 (4)	2	5	2.5	6.4 6.0	3 (29)	3 (29)	1 (14)	6 (43)	0.54 0.46	7/14 (50)	0/14 (0)
All	27 (24)	7	21	3.0	6.9 7.0	17/27 (63)	4/27 (15)	6/27 (22)	20/54 (37)	0.39 0.25	20/54 (37)	11/54 (20)

* Number of eyes with visual recovery.

Number of eyes with best-corrected visual acuity (BCVA) ≥ 0.5 or < 0.05 in Snellen decimal.

Abbreviations: BCVA, best corrected visual acuity; f, female; m, male.