Very Early Onset of Leber's Mitochondrial Optic Neuropathy in Pediatric Females: Case Report and Review of the Literature

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Abstract

Background

Leber's hereditary optic neuropathy is a rare mitochondrial disease that usually begins in the second/third decade of life and affects generally young adult males. The information is scarce on the female phenotype particularly when onset is at a very young age and the diagnosis is challenged by other more frequent conditions. Aim of this study is to highlight the pediatric female phenotype by a literature review and by adding a new case.

Methods

The literature search was conducted on Pubmed in the period September 2020-February 2021 using "Child", "Leber Hereditary Optic Neuropathy", "females" "girls" keywords. We add a three years old girl with genetically confirmed Leber's hereditary optic neuropathy.

Results

55 of 968 articles reported pediatric in girls accounting for 226 cases, male to female ratio 1,8:1. Mean age at onset was 11 years. The onset at the age of 3 years was described in only 3 girls, including our case. Acute bilateral mild visual impairment was the most common clinical presentation, associated to papilledema in 14% of the cases who underwent fundus oculi examination. Partial visual recovery occurred in 50% (30/60). Idebenone treatment was administered in 5/30.

Conclusion

LHON is extremely rare in very young females and represents a diagnostic challenge for the pediatrician. It should be considered even in young girls with acute-subacute visual loss, bilateral pseudo-papilledema, VEP changes non responding to steroid therapy.

What Is Known

Leber's hereditary optic neuropathy usually affects young males in second-third decade of life with female/male ratio of 1:5. Pediatric onset is rare and poorly described: acute onset is the most frequent modality of presentation and papilledema can occur.

What Is New

In pediatrics, the gender difference is less evident, in our narrative review the female/males ratio is 1:1,8. Mean onset age in females is 11 years with minimum onset age of 3 years, described in only three cases worldwide.

Introduction

Leber hereditary optic neuropathy (LHON) is a mitochondrial genetic disease that leads to acute or subacute painless loss of vision, over a period of weeks to months. Affected individuals usually carry one of the three major mitochondrial DNA (mtDNA) mutations (ND1 3460G>A, ND4 11778G>A, ND6 14484T>C), but more than 30 types of mtDNA mutations play a role in disease expression. The penetrance of these genetic defects is incomplete and influenced by the phenomenon of heteroplasmy, by other modulatory genes and also by epigenetic factors, making genetic counseling extremely difficult [1]. Genic mutations cause altered oxidative phosphorylation in complex 1 of mitochondrial respiratory chain with increased levels of reactive oxygen species and apoptosis of retinal ganglion cells and their axons.

LHON occurs in about 1: 30000 people in the general population [2]. Males are mostly affected in their second or third decade of life: patients with classic LHON experience visual loss between 15 to 35 years of age, childhood onset occurs in 11,5% of the cases [3]. The age limit for childhood onset is variable according to different studies: mean age at onset of the disease is about

6,8 years of age (range 2-11y) in European centers and about 10 years (mean 8,7 years, range 3,4-17) in the Chinese population [4,5,6]. In childhood also, males are more affected than females [4,6]. The mean onset age in girls is not described.

The clinical presentation of pediatric LHON allows to distinguish three forms of disease: acute, slowly progressive and subclinical.[5] The information is scarce on the female phenotype particularly when onset is at a very young age [50,58].

When ultra-rare phenotypes are involved, the diagnosis is challenged by other similar and more frequent pediatric neurological and neuro-ophthalmological conditions such as optic nerve drusen, optic neuritis and other optic neuropathies [105,108]. Treatment with Idebenone has been shown to contrast progression of the disease towards blindness in many patients, but it has to be started early in the course of the disease [112]. The aim of this study is to highlight the young female phenotype of LHON by an extensive literature review and by adding a new case with very early onset, as a contribution to early recognition of the disease.

Methods

We report a three years old girl with genetically confirmed LHON. Therapeutic and diagnostic acts and the analysis of the clinical case were performed with the consent of her parents.

Moreover, we conducted a literature review looking for pediatric cases of LHON occurring in females. Our search was performed in PubMed, from inception up to 20 September 2020, with the following search terms combinations: “Childhood Leber Hereditary Optic Neuropathy AND females”, “Leber mitochondrial Optic Neuropathy in pediatrics AND females” and also “Leber Hereditary Optic Neuropathy AND girls” to consider also adult female cases with pediatric onset. All the articles were screened reading titles, abstract and, as needed, text.

Among eight articles excluded, full text remained unavailable, so we extracted available information from the abstract [62-69].

After duplicates removal, 968 articles were analyzed. All the articles with lack of clinical data, lack of information about age at onset, impossibility of extracting information separately by sex and age were excluded, as well as cases regarding only boys and with adult onset only [70-103]. Fifty-five articles were eligible and were analyzed to extract relevant clinical information. [1,4-10,14,16-61] (Fig.1).

Tables 1: 55 articles about LHON occurring in females [1,4-10,14,16-61]

Article	Type of study	Pediatric LHON (n°.)	Female cases (n°.)	Age at onset or mean (y)	Type of onset	Neuro-ophthalmological data	Recovery
1.[16]	Case series	1	1	8	No data available	Decline in visual acuity	No data available
2.[17]	Retrospective study (19)	6	2	I: 15 II: 10	Acute onset	I: visual acuity at nadir (RE:LE) 0,005 log MAR in both (moderate visual impairment) II: visual acuity at nadir (RE:LE): 0,1 log MAR in both (mild visual impairment)	No Partial
3.[18]	Perspective study (53)	7	3	I: 7 II: 11 III: 14	I: slowly progressive II: subclinical III: acute	Fundus oculi: unknown peripapillary microangiopathy	I: partial II: partial III: No
4.[10]	Case report (LHON plus)	3	1	11	Acute bilateral onset	Visual acuity: RE 0,1 LE 0,08 logMAR(mild: moderate) Goldmann Perimetry: Central scotomas Fundus oculi: Atrophy of optic disc Normal PEV	No
5.[19]	Retrospective study (9)	8	3	10	Acute onset	I: Visual acuity (RE: LE):0,1: 0,3 logMAR (mild: mild) Goldmann perimetry: paracentral scotoma in both eyes. Fundus oculi: pale optic discs temporally VEP: delayed P100 latecies for large check sizes and no recordable responses for small check sizes	I: no II: No with 18 months Idebenone therapy III: no with Idebenone therapy (discontinued)

						II: Visual acuity: (RE: LE): 0,1:0,1 logMAR (mild: mild) Goldmann perimetry: I central scotoma in OD. Fundus oculi: hyperemia and turgor of the optic papilla. III: Visual acuity: (RE: LE):0,2: 0,1 (mild: mild) Goldmann perimetry: central scotoma in both eyes. Fundus oculi: hyperemic disc and peripapillary telangiectatic microangiopathy	
6.[20]	Retrospective study (19)	6	2	I: 3 II: 17	No data available	I: Visual acuity(RE:LE): 0,4:0,1 logMAR II: Visual acuity(RE:LE): 0,5: 1 logMAR	No data available
7. [21]	Case report (3)	3	1	15	Acute onset	Visual acuity (RE:LE): 0,2:0,1 (mild) Fundus oculi: pale optic disc Goldmann perimetry: central scotomas in both eyes with small fenestrations	No with therapy
8. [22]	Case report (2)	1	1	9	Acute onset	Fundus oculi: bilateral optic disc atrophy in both eyes Goldmann perimetry: central scotomas in both eyes	Spontaneous partial recovery
9. [23]	Retrospective study (32)	12	2	I: 15	Acute onset	I: Visual acuity(RE:LE): CF/CF (profound visual impairment)	No data available

				II: 16		Color vision: 0/12 bilaterally Fundus oculi: bilateral optic disc hyperemia in both eyes, peripapillary microangiopathy Visual fields test: central scotomas in both eyes II : Visual acuity (RE:LE): 0,1 logMAR bilaterally (mild impairment) Color vision: 5/12 bilaterally Fundus oculi: bilateral optic disc hyperemia in both eyes peripapillary microangiopathy Visual fields test: central scotomas in both eyes	
10. [24]	Retrospective study: (3)	1	1	17	Slowly progressive	Visual acuity slowly decreasing in 20 years until CF:CF Fundus oculi: bilateral optic disc atrophy in both eyes Visual fields test: central scotomas in both eyes	No
11. [7]	Case report	1	1	6	No data available	Decline in central visual acuity	No data available
12. [25]	Case report	2	1	12	Acute onset	Visual acuity: RE finger counts, LE: +1,3 logMAR Goldmann perimetry: bilateral central scotomas. Fundus oculi: hyperemia and turgor of the optic papilla.	Partial visual recovery with steroids.
13. [26]	Retrospective study	4	3	2: 10	Acute onset	I: Visual acuity (RE:LE): 0,02/0,02	No data available

				1: 13		logMAR, Fundus oculi: optic disc pale II: Visual acuity (RE:LE): 0,1 logMAR /, CF*, Fundus oculi: optic disc pale III: Visual acuity (RE:LE): 0,05:0,05 logMAR, Fundus oculi: optic disc pale	
14. [4]	Retrospective study: (180)	14	1 1	10 No data available	Acute bilateral LHON Slowly progressive LHON	BCVA* (RE*: LE*): 0,3 +/- 0,3 logMAR (mild-mild) Fundus oculi: Diffuse optic disc atrophy without microangiopathy OCT: diffuse RNFL* thinning BCVA (RE/LE): 0,6 +/- 0,1 logMAR (mild:mild) Fundus oculi: Atrophy of temporal sector of optic disc, variable microangiopathy OCT: RNFL* reduction in temporal quadrant	No Partial visual recovery
15. [9]	Case report (LHON plus)	1	1	17	Acute onset	Goldmann perimetry: bilateral central scotomas. Fundus oculi: bilateral optic atrophy, but not peripapillary telangiectasia and retinal degeneration.	No data available
16. [27]	Case report	2	2	I: 3	Acute onset	I: visual acuity (RE:LE): 0,5:0,15 logMAr (normal: mild)	Mild improvement: visual acuity (RE:LE) 0,7:0,2 logMAR 14 years later

				II: 4		Fundus oculi: slightly pale optic disc VEP: reduced amplitude II: : visual acuity (RE:LE): 0,15: 0,12 logMAR (mild:mild)	Mild improvement: visual acuity (RE:LE) 0,2:0,7 logMAR 14 years later
17. [28]	Retrospective study: (13)	10	2	I: 13 II: 14	Acute onset	I: visual acuity RE:LE : 0,02/0,01 logMAR (profound visual impairment) II: visual acuity RE:LE 0,05/0,04 logMAR (moderate: severe)	No data available
18. [29]	Retrospective study: (5)	3	2	I: 7 II: 14	Acute onset	I: visual acuity (RE: LE): 0,12/0,4 logMAR (mild visual impairment) Goldmann perimetry: large centrocecal scotoma in both eyes II: 0,05/0,1 moderate visual impairment Fundus oculi: vascular tortuosity of central retinal vessels, microangiopathy in both eyes, no reflex on fovea on both eyes Visual field test: large centrocecal scotoma in both eyes VEP: decreased amplitude and delayed latencies in both eyes	No data available
19. [30]	Retrospective study (15)	4	2	I: 14	Acute onset	Visual acuity (RE:LE): 0,1:0,08 logMAR (mild: moderate)	No data available

				II: 15		Fundus oculi: vascular tortuosity of central retinal vessels, microangiopathy in both eyes Visual field test: large centrocecal scotoma in both eyes VEP: decreased amplitude and delayed latencies in both eyes, bilateral hearing loss Visual acuity (RE:LE): 0,06:0,06 (moderate: moderate)	
20. [31]	Retrospective study; (25)	5	1	10	Acute onset	Visual acuity: 0,12/0,2 logMAR (mild: mild)	No data available
21. [32]	Case report	1	1	12	Acute onset but atypical presentation (convergent strabismus, horizontal nystagmus in condition of progressive ataxia, progressive ophthalmoplegia, referactary epilepsy)	Visual acuity: 0,05:0,05 (moderate: moderate) Field visual test: centrocecal scotomas in both eyes Fundus oculi: bilateral optical disc atrophy	No data available
22. [33]	Case control study:	1	1	12	Acute bilateral onset	Visual acuity: +1,00 logmar bilaterally (20/200=0,1) Fundus oculi: Diffuse Optical Atrophy Goldmann Perimetry: Centrocecal scotomas Modest horizontal nystagmus	No
23. [34]	Retrospective study: (18)	15	9	I: 6 II, III: 9	No data available	Visual acuity (RE:LE): I: 0,8/0,8 logMAR	I, III, V, VII, VIII, IX : partial spontaneous visual recovery

				IV, V: 10 VI: 11 VII: 12 VIII: 15 IX: 17		II: 0,08/0,05 logMAR III: 0,6/0,6 logMAR, paracentral scotomas IV: 0,04/0,04 logMAR central scotomas V: 0,8/0,8 logMAR VI: 0,8/0,3 logMAR paracentral scotomas VII: 0,8/0,8 logMAR VIII: 1/0,6 logMAR paracentral scotomas IX: 0,6/0,6 logMAR	II, IV, VI: No recovery
24. [35]	Retrospective study	3	1	14	Acute onset	Visual acuity (RE:LE): 0,1:0,1 logMAR (mild: mild) Goldmann perimetry: centrocecal scotoma Fundus oculi: optic disc pale in temporal sector	No data available
25. [36]	Retrospective study: (14)	9	1	15	Acute onset: first in RE and then in LE	Visual acuity (RE:LE): 0,1:0,1 (mild: mild)	No data available
26. [1]	Retrospective study: (9)	6	2	I: 9 II: 15	Acute onset	Visual acuity (RE: LE): I: 0,3/0,12 (mild: mild) II: 0,2/0,10 (mild:mild)	No data available
27.[37]	Retrospective study: (61)	15	2	Both 14	No data available	No data available	No data available
28 [38]	Retrospective study: (29)	14	9	I, II: 7 III: 8 IV, V, VI: 9 VII: 10 VIII: 12 IX: 16	No data available	Visual acuity (RE: LE): I: 0,01/0,01 logMAR (profound) II: 0,12/0,6 logMAR (mild: mormal) III: 0,01/0,01 logMAR (profound)	No data available

						IV: 0,08/0,05 logMAR (moderate) V: 0,1/0,6 logMAR (mild: normal) VI: 0,4/0,12 logMAR (normal:mild) VII: 0,25/0,5 logMAR (mild: normal) VIII: 0,3/0,25 logMAR (mild: mild) IX: 0,08/0,09 logMAR (moderate: moderate)	
29. [39]	Retrospective study	25	10	I, II, III, IV, V: 12 VI, VII, VIII, IX: 17 X: 14	No data available	No data available	No data available
30. [40]	Case report LHON-MELAS overlap syndrome	1	1	11	Acute onset	Visual acuity: CF in both eyes (profound: profound) Fundus: RE: dilatation and tortuosity of all branches of central retinal vein, intraretinal hemorrhage, hyperemic disc LE: pinkish optic disc, mild tortuosity of small and medium arterioles Fluorescein Angiography: RE: delayed venous filling LE: normal	Partial recovery with Q10 coenzyme
31. [41]	Retrospective study: (9)	4	2	I: 8 II. 15	Acute onset	Visual acuity (RE: LE): I: 0,1/0,1 (mild: mild) II: 0,05/0,05 (moderate: moderate)	No data available
32. [42]	Case report: (5)	4	2	I: 7	Acute onset	Visual acuity (RE:LE):	Partial spontaneous recovery

				II: 12		I: 0,02:0,3 logMAR (severe: mild) II: Not available	
33. [43]	Retrospective study: (34)	15	3	I: 14 II: 11 III: 5	No data available	No data available	No data available
34. [44]	Observational Perspective Study: (26)	11	3	I: 6 II: 5 III: 14	No data available	I: CF/CF (profound) II: 0,1/0,1 logMAR (mild) III: 0,05/0,05 logMAR (moderate)	No data available
35. [45]	Retrospective study: (34)	3	3	I: 6 II: 4 III: 14	Acute onset	Best Visual Acuity (BCVA) (RE:LE): I: RE 0,125 LE 0,25 logMAR (mild: normal) II: RE 0,6 LE 0,6 logMAR (normal) III: RE 0,8 LE 0,6 logMAR (normal)	I: no s recovery II, III: partial spontaneous recovery
36. [46]	Retrospective study: (9)	5	1	15	Acute onset	Visual acuity: CF both (profound)	Partial visual recovery
37. [47]	Retrospective study: (16)	5	2	I: 15 II: 17	Acute onset	Visual acuity (RE:LE): I: 0,03: 0,05 logMAR (severe: severe) II: 0,06: 0,1 logMAR (moderate: mild)	No data available
38. [48]	Case report: LHON-MELAS overlap	1	1	12	Acute onset: loss of vision in both eyes. One month later, vertigo, anhedonia, hearing loss, migraine attack	Visual acuity: RE: 0,2 LE: 0,03 logMAR (mild:severe) Fundus oculi: both optic nerves pale Fundus autofluorescence: bilateral hyperfluorescent optic nerve deposits Standard automated perimeter: severe	No data available

						bilateral visual loss OCT: RNFL thickening (3,54 mm) VEP: reduced amplitudes with prolonged P100 wave latencies bilaterally.	
39. [49]	Perspective study: (9)	8	2	I F: 8 II F: 9	Acute onset	I: Visual Field Index (VFI) * 0% II: VFI* 3%	Partial recovery with gene therapy
40. [50]	Clinical trial (16)	12	3	I: 8 II: 9 III: 7	No data available	I: BCVA RE: 0,9, LE: 1,2 logMAR II: BCVA RE:0,2, LE:0,2 logMAR III: BCVA LE:2 (normal) logMAR	No improvement with gene therapy at 12 months
41. [51]	Retrospective study: (105)	36	20	I: 7 II: 9 III: 11 IV, V, VI, VII, VIII, IX, X, XI: 15 XII, XIII: 13 XIV, XV, XVI: 16 XVII, XVIII, XIX, XX: 17	No data available	No data available	No data available
42. [52]	Retrospective study: (101)	45	13	I: 5 II: 6 III: 10 IV: 11 V, VI: 13 VII: 14 VIII IX: 15 X: 16 XI XII XIII: 17	No data available	Visual acuity (RE: LE) : I: hand movement profound visual impairment II: 0,1:0,1 logMAR moderate impairment III: 0,02:0,03 logMAR severe impairment IV: 0,08: 0,06 logMAR moderate impairment V: 0,15: 0,15 logMARmild impairment VI: 0,2:0,15 logMAR mild impairment	No data available

						VII: 0,1:0,1 logMAR mild impairment VIII: 0,03:0,05 logMARSevere impairment IX: CF (profound impairment) X: 0,02: 0,25 logMAR severe impairment XI: 0,1:0,2 logMAR mild impairment XII: 0,06: 0,1 logMAR moderate impairment XIII: 0,1:0,1 logMAR mild impairment	
43. [6]	Perspective study: (119)	89	10	Median age: 10,6	Acute onset: 54/89	Visual acuity: (RE:LE) 0,06 ± 0,46 logMAR Fundus oculi: bilateral optic nerve edema or hypereaemia with/without telangiectatic vessels; temporal optic pallor with vascular tortuosity in both eyes; temporal optic pallor with microvascular tortuosity in the right eye and optic nerve hyperemia with telangiectatic vessels in left eye. OCT: greater RNFL thickness in inferior and superior quadrants	No data available
				Median age: 9,8	Slowly progressive onset: 35/89	Visual acuity 0,12 ± 0,03 logMAR Fundus oculi: temporal optic atrophy without changes in the vessels in both eyes; diffused atrophy of the optic disk in both eyes.	No data available

						OCT: reduced RNFL thickness in temporal quadrant VEP: from a serious conduction defect to the absence of a waveform.	
44. [14]	Case report:	2	2	Median age: 7,5	Acute onset	Visual acuity (RE:LE): I: 0, 25/0,13, logMAR II: 0,5/0,8 logMAR Fundus oculi: pallor of optic papilla	I no visual recovery II: partial visual recovery (Visual acuity RE:LE : 0, 6/0,8)
45. [53]	Perspective observational study: (103)	No specific datas about childhood LHON	23	Range: 24+/-10	Acute onset: bilateral visual impairment	BCVA: 0,1+/-0,03 logMAR in both eyes (mild)	No data available
46. [5]	Retrospective study: (27)	27	5 2	Median age: 8,2 Median age: 7,5	Acute onset (17) Slowly progressive onset (4)	BCVA (RE:LE): 2:Light perception (profound) RE: 0,03 LE: 0,03 logMAR(severe-severe) RE: 0,79 LE: 0,79 logMAR (normal-normal) RE: 0,91 LE: 1,00 logMAR (normal-normal) BCVA (RE:LE): RE: 0,17 LE: 0,02 logMAR (mild: severe) RE: 0,17 LE: 0,25 logMAR (mild: mild)	no visual recovery
47. [54]	Retrospective study: (44 pediatric cases of	12	2	No data available (certainly<14)	No data available	Visual acuity at 15 y: 0,8 +/- 0,4 in both eyes (Normal)	No data available

	optic neuropathy)						
48. *[55]*	Perspective study (9)	8	2	I F: 8 II F: 9	Acute onset	I: VFI 0% II: VFI 3%	Partial recovery with gene therapy
49. [56]	Retrospective study: (352)	5	3	I: 10 II: 17 III: 15	No data available	I: moderate visual impairment II: mild visual impairment II: mild visual impairment	No data available
50. [57]	Case series (10)	2	1	16	Acute onset followed by Visual allucinations without cognitive impairment	Visual acuity: light perception and hand movements in both eyes (profound)	No data available
51. [58]	Retrospective study on gene therapy efficacy: (53)	No specific datas about childhood LHON	5	16 +/-5	No data available	Improving with gene therapy: baseline BCVA 1,94 logMAR +/-0,31 (normal) Not improving with gene therapy: Baseline BCVA 1,76 +/- 0,42 (normal)	2F improvement with gene therapy 3F no improvement with gene therapy
52. [59]	Case report	1	1	11	Acute onset: poor vision LE	Visual acuity at onset: LE 0,02 logMAR Automated perimetry: central scotoma in LE Normal OCT VEP: reduced P50 amplitude and normal N95 in the left eye	Stable at 5 year with Idebenone
53.[8]	Retrospective study: (64)	17	6	I: 6 II:6 III: 4 I: 7 II: 4 III: 13	Subacute (3F) Slowly progressive (3F)	I: Visual acuity: BCVA RE: 0,2 LE: 0,4 logMAR (mild: normal) II: Visual acuity: BCVA RE: 0,125 LE: 0,2 logMAR (mild: mild) II: Visual acuity: BCVA RE: 1 LE: 0,4 logMAR (normal: normal)	I: no recovery II: no III: spontaneous recovery I: no II: spontaneous recovery III: no

						I: Visual acuity: BCVA RE: 0,125 LE: 0,6 logMAR (mild: normal) II: Visual acuity: BCVA RE: 0,125 LE: 0,16 logMAR (mild:mild) II: Visual acuity: BCVA RE: 0,8 LE: 0,62 logMAR (normal: normal)	
54. [60]	Retrospective study: (16)	13	1	16	Acute onset	BCVA (RE:LE): 0,1 logMAR / finger counts (mild: profound)	Partial recovery: 0,1/0,06 logMAR
55. [61]	Retrospective study: (1520)	123	34	<5 Y: 1/1 5-9Y: 1/3	No data available	No data available	No data available

Abbreviations: BCVA*: best corrected visual acuity RNFL*: Retinal Nerve Fiber Layer RE*: right eye LE*: left eye CF*: counting fingers HM*: hand movement VFI*: Visual Function Index

Results

Case Report

A 3-years-old girl was admitted due to recent onset of visual impairment. The parents reported normal previous psychomotor development, growth and visual behavior. Previous personal history was not relevant, including pharmacological therapies. Family history was silent for visual disturbances and neurological disorders. In the previous months parents noticed that the girl brought her eyes close to the table during drawing and she turned the head to favour vision with her left eye; she didn't follow images on a screen and when the right eye was covered she complained of not seeing anything. She never complained headache and vomiting. On arrival she had poor visual acuity (right eye less than 1.0 logMAR, left eye equal to 0,4 logMAR), the neurological examination was normal with the exception of vision loss. The cognitive function was normal with the exception of visual attention skills defect. The fundus oculi examination revealed a raised optic papilla with blurred edges more pronounced in the right eye and tortuous vessels, consistent with bilateral moderate papilledema. Brain magnetic resonance imaging (MRI) was normal except for mild bilateral flattening of the posterior sclera, associated with mild perineural cerebrospinal fluid in the optic nerve sheet. The ultra-sounds of the posterior eye and optic nerve excluded the optic nerve Drusen. In the suspicion of pseudotumor cerebri, a lumbar puncture was performed and revealed an opening pressure of 200 mmH2O (normal range100-200 mmH2O), with normal spinal fluid chemical-physical and biochemical parameters. Blood exams, serological investigations and Angiotensin Converting Enzyme levels were normal. Acetazolamide therapy was started with transient improvement of optic disk swelling. In the following days visual acuity had worsened (right eye 0,1 logMAR, left eye 0,8 logMAR) and eccentric fixation at distance was noted. Visual evoked potentials were performed and showed bilaterally decreased amplitudes and delayed latencies of the P100 cortical response. Cerebrospinal fluid oligoclonal bands and serum antibody testing for aquaporin-4 and myelin oligodendrocyte glycoprotein were all negative. In the hypothesis of optic neuritis, Methylprednisolone 30 mg/kg bolus was administered for 3 days, followed by a tapering course of corticosteroids orally administered. Despite steroid treatment, visual evoked potentials worsened sequentially from right to left eye. A second brain and orbits MRI performed two months later was normal, except for symmetrical signal alteration in the black substance of the midbrain. Considering the clinical and electrophysiological deterioration during steroid treatment, atypical for optic neuritis, despite the female sex and young age, we hypothesized LHON. The molecular analysis of mitochondrial DNA found the homoplasmic mutation 3460G>A in gene MT-ND1 suggestive for LHON. The mother and sister were carriers of the same variation, in the absence of clinical symptoms. The exome analysis targeted on optic neuropathy phenotype, to rule out co-occurrence of other forms of optic neuropathy was negative.

Optical coherence tomography (OCT) showed a marked reduction in thickness of retinal nerve fiber layer in all areas *(Fig.2).* Four months after disease onset, off-label Idebenone therapy was started following written informed consent by the parents, to reduce mitochondrial dysfunction. The brain MRI one year after the first one was completely normal.

At follow up three years later, during Idebenone therapy, the visual acuity improved and was equal to 0,22 logMAR in the left eye and 0,7 logMAR in the right eye. Colour vision tested with Ishihara tables showed an incomplete red-green colour deficiency while contrast sensitivity remained abnormal. Visual field testing confirmed the presence of a central scotoma. Visual fatigue, crowding effect and glare were unchanged relevant symptoms hampering daily activities. Visual evoked potentials were stable compared to the previous ones and the OCT showed a small progression of the atrophy of retinal ganglion cells (*Fig 3).*

Visual rehabilitation in synergy with the family and teachers supported the child in the development of compensatory strategies and multisensory integration. The girl developed compensatory posture with head tilted on the right shoulder, right eye exotropia and hyperfunction of left ocular muscles. At the age of 5 a drawing done by our child shows her self-perception (*Fig.4*).

Literature Review

We identified 55 articles about LHON occurring in females [1,4-10,14,16-61], they are summarized in Table 1. Sixteen were case reports, 32 were retrospective studies and 7 were prospective studies. In total we identified 626 cases of LHON with onset before 18 years. Of these, 226 were females with a male to female ratio of 1,8:1. The mean age at disease onset was 11 years The minimum onset age was 3 years, described in only two cases (1,3%): all other reported females were older at onset of the visual symptoms [50,58].

The onset modality of LHON was described in 91 out of 226 females (41%): the acute onset occurred in 79/91 (86,5 %), subclinical or subacute onset in 4/91 (4,5%) and slowly progressive onset in 8/91 (9%).

The severity of visual impairment was reported at diagnosis in 118 girls (52%). In the total population, visual impairment was bilateral with sequential involvement of right and left eye. The visual acuity was normal in 24 right eyes (RE) (20%) and in 23 left eyes (LE) (19,5%). The visual impairment was mild (mild =0.3–0.1logMAR) in 65 RE (55%) and 61 LE (52%); it was moderate (0,1-0,05 logMAR) in 12 RE (10%) and in 13 LE (11%); it was severe (0,05-0,02logMAR) in 8 RE (7%) and 10 LE (8,5%); it was profound (<0,02logMAR, counting fingers or light perception) in 9 RE (8%) and in 11 LE (9%).

The Goldmann perimetry was reported in only 13/226 females (6%), the main finding was central scotomas. Fundus oculi was reported in 36/226 females (16%): - atrophy of the entire optic disc in 6/36; - edema and hyperemia of optic disc in 5/36 (cases with acute onset); - atrophy of temporal sector in 1/36 (cases with slowly progressive onset); - pale optic disc in 9/36; - isolated microangiopathy in 5/36. Edema and tortuous vessels in acute stage of LHON and optic pallor or atrophy in slowly progressive LHON was seen in 10/36.

The OCT was described in 14/226 females (6%): those with acute onset showed diffuse thinning of retinal nerve fiber layer while those with slowly progressive onset showed atrophy of the temporal sector, in 1 case the OCT was normal. The visual evoked potentials (VEPs) were reported in 18/226 (8%) of the girls and were characterized, at disease onset, by reduced amplitude and delayed latency.

Data about visual recovery were reported in 27 articles comprising 60/226 females (26,5%). Sixteen out of 60 females (26,5%) received a specific therapy: 5 were treated with Idebenone, 10 with gene therapy and 1 with steroids. Among those treated with Idebenone, 3/5 had no visual recovery and 2/5 had no worsening of visual acuity but stabilization or improvement of the visual defect. Ten underwent gene therapy: 7/10 (70%) recovered and 3/10 (30%) had no visual recovery. One female received steroids without improvement at a follow up performed 8 years later. Forty-four (73,5%) did not receive treatment: 23/44 had no recovery while 21/44 showed spontaneous partial recovery of visual function. Partial visual recovery, with or without therapy, globally occurred in 30/60 (50%) girls.

Discussion

This study reports the third case of genetically confirmed LHON in a pediatric female with very early age at onset and adds an extensive review of the literature on pediatric female cases. In our patient the onset modality of LHON was with abnormal visual behavior and papilledema at three years of age. The Idebenone treatment allowed slight recovery of vision, followed by stabilization during a 5 years' follow-up. Research on pediatric LHON is scarce, particularly in females and lacks of systematic phenotype description, particularly at symptoms onset.

In our review of pediatric girls, the mean age at symptoms onset was 11 years, probably for the predominance of Asiatic literature reporting a more advanced onset age in females [4,5,6,7].

In adults the female/male ratio is 1:5 [4,5]. The male prevalence can be explained by a modulatory effect on mitochondrial expression due to some loci on the X-chromosome (*DXS8090-DXS1068, DXS1068-DXS8016*), the life style (smoking exposition) and hormonal differences [104,105]. By contrast, in pediatrics, this gender difference is less evident. In our study the female/male ratio was of about 1:1,8. Diversity between pediatric and adult age is explainable by being more heavily genetically determined by nuclear modifiers, and by lower hormonal and environmental influences in childhood LHON [4,5,13,104].

Our literature review highlights that the clinical features at onset, are scarcely described in girl, available only in 41% of the cases, since the focus is mainly on genetic characterization.

The onset modality of LHON was not specified in about half of the girls. The acute onset was the far most frequent mode of presentation, characterized by sequentially bilateral visual loss (reported in 86,5% of our literature review) [1,4-10,1416-61] and also in our case. The visual loss was mild or moderate in the majority of cases. The fundus oculi examination was available in only 16% of the cases and the most frequent presentation was acute with edema of the optic disk.

In very young children the visual loss may be undetected when monocular or not severe, Moreover, the diagnostic tools available in adults for the characterization of visual loss are difficult to perform at a young age. The onset in girls as young as 3 years is described in only three cases in the literature, including our patient. One of the other two cases was a girl presenting with exotropia and bilateral visual impairment (left eye more than right eye): her fundus examination at onset revealed pale optic disc, VEPs were similar to ours and she never recovered [50].

In the second case, the clinical information is very scarce and reports only that the girl had a mild visual impairment at onset [58].

The very early onset LHON presentation challenges the pediatricians, particularly if it includes the pseudo-papilledema.

Indeed, the differential diagnosis of acute subacute visual loss includes a variety of more frequent medical conditions as well as optic neuritis or other forms of optic neuropathy [105].

In the presence of optic disc edema, the first differential diagnosis is between papilledema due to raised intracranial pressure and pseudo-papilledema, an elevation of the optic disc secondary to local underlying structural conditions, in the absence of raised intracranial pressure. No gold standard instrumental test exists to distinguish between papilledema and pseudo-papilledema [105]. Clinically, patients with papilledema rarely present a rapidly progressive visual loss and their color vision is typically spared. Furthermore, the papilledema is often associated to signs and symptoms of raised intracranial pressure such as morning headache, diplopia, pulsating tinnitus and vomiting. The differential diagnosis requires brain and spinal magnetic resonance imaging to search for the presence of intracranial or spinal mass lesions, cerebral sinovenous thrombosis, and the nonspecific indicators of pseudotumor cerebri (posterior globe flattening, distention of the cerebrospinal fluid space, empty or partially empty saddle, and transverse venous sinus stenosis)[106]. In patients with normal MRI, the lumbar puncture may be used to evaluate increased opening pressure, suggesting raised intracranial pressure [105].

The second important differential diagnosis, in cases of papilledema without elevated cerebrospinal fluid pressure (pseudo-papilledema), is with optic nerve drusen, optic neuritis and other optic neuropathies and requires other diagnostic tools such as visual field examination, OCT, optic bulb ultrasounds and visual Evoked Potentials (VEPs). Our literature search retrieved very few data based on these diagnostic tools, probably because they are difficult to perform and interpret in young children [107,108,109].

Among the differential diagnoses of LHON, the most challenging is anterior optic neuritis. Clinically, pain during eyes movements, dyschromatopsia and afferent pupillary defect orient towards optic neuritis. However, afferent pupillary defect is seldom seen in pediatrics because optic neuritis is usually bilateral and pain or dyschromatopsia are difficult to evaluate at a young age [105]. In these cases, VEPs can be useful even in very young children. In acute LHON, they show amplitude decrease and delayed latency of the P100 peak. Shortening of P50 is an additional feature in those with LHON history longer than 3 months [12]. By contrast, n optic neuritis, VEPs show a predominant delay in the latency of the response, while amplitude is more variably affected, but the most important differential feature is the recovery of optic neuritis but not of LHON, following steroid therapy [12,110].

The LHON diagnosis needs to be confirmed by detection of mutations in mtDNA: methods such as direct DNA sequencing, polymerase chain reaction, restriction fragment length polymorphism and next generation sequencing techniques can be used to find mtDNA mutations [13]. One of the possible reasons for the rarity of disease onset at very early age is that the significant complex I dysfunction, needed for mitochondrial related optic nerve damage, requires time and usually does not occur before school-age [102].

The diagnosis was a challenge in our case also because the family history was uneventful even if, for the incomplete mitochondrial disorders penetrance, the mother and sister were healthy carriers of the same mutation [104].

The natural history of LHON is characterized by progressive loss of visual function, although the advent of Idebenone treatment provided recovery or stabilization in 2/5 patients [27,39]. The present study of LHON occurring in girls, found reported outcome in 26,5% of the cases. About half of them had visual recovery or stabilization of vision, only a minority received Idebenone (8%) or gene therapy (16%), with variable success. An early therapy can arrest the progression of visual disease; Idebenone has been approved in 2015 by European Union [14,111,113]. Its use is off-label before 12 years of age. It is a strong antioxidant, inhibitor of lipid peroxidation an also interacts with electron transport chain facilitating mitochondrial electron flux bypassing complex I.

In our patient Idebenone treatment was started before the evolution from papilledema to optic disk atrophy and visual function did not deteriorate during the following 5 years.

Nowadays, early diagnosis and starting early antioxidant treatment is the only way to counteract deterioration of visual function while gene therapy is on the way.

The main limitations of the present study are the heterogeneity of the collected patients and the incomplete information on some clinical data, even if we used stringent selection criteria. However, this is the first study reporting specific clinical information on the population of pediatric females affected by LHON. To rise clinical awareness on the rarest phenotypes of LHON such as that of young females has important implications for early diagnosis and effective management.

Conclusions

LHON in the female gender, particularly with early pediatric onset, is extremely rare. Only three cases, including ours, are described as early as at three years. The pediatrician facing a very young girl with acute-subacute visual loss, bilateral pseudo-papilledema, VEP changes non responding to steroid therapy should think to LHON early in the course of the disease after having excluded other more frequent causes. Early and timely diagnosis is important to preserve vision.

Abbreviations

Best Corrected Visual Acuity (BCVA), Counting Fingers (CF), Intra-Cranial Pressure (ICP), Leber Hereditary Optic Neuropathy (LHON), left eye (LE), Magnetic Resonance Imaging (MRI), mitochondrial DNA (mtDNA), Optical Coherence Tomography (OCT), Retinal Nerve Fiber Layer (RNFL), right eye (RE), Visual Evoked Potentials (VEPs).

Declarations

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Conflict of interest/Competing interest

The authors declare that they have no conflict of interest.

Availability of data and material

The authors confirm that the data supporting the finding of this study are available within the article.

Author's Contribution

A.S., C.M., S.T. conceptualized the review., S. T. reviewed the literature, evaluated articles for eligibility. C.C, A.S. gave resources about clinical case. C.C, C.M. did critical review of manuscript. S.T., C.M wrote the manuscript. A.S. and F.P. reviewed the article for important intellectual content. A.S and C.M supervised the work.

Ethical standards

No ethical approval is required

Consent to participate

Parents gave their informed consent prior to their inclusion in the study.

Consent for publication

Parents gave their written informed consent prior to publication.

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Figures

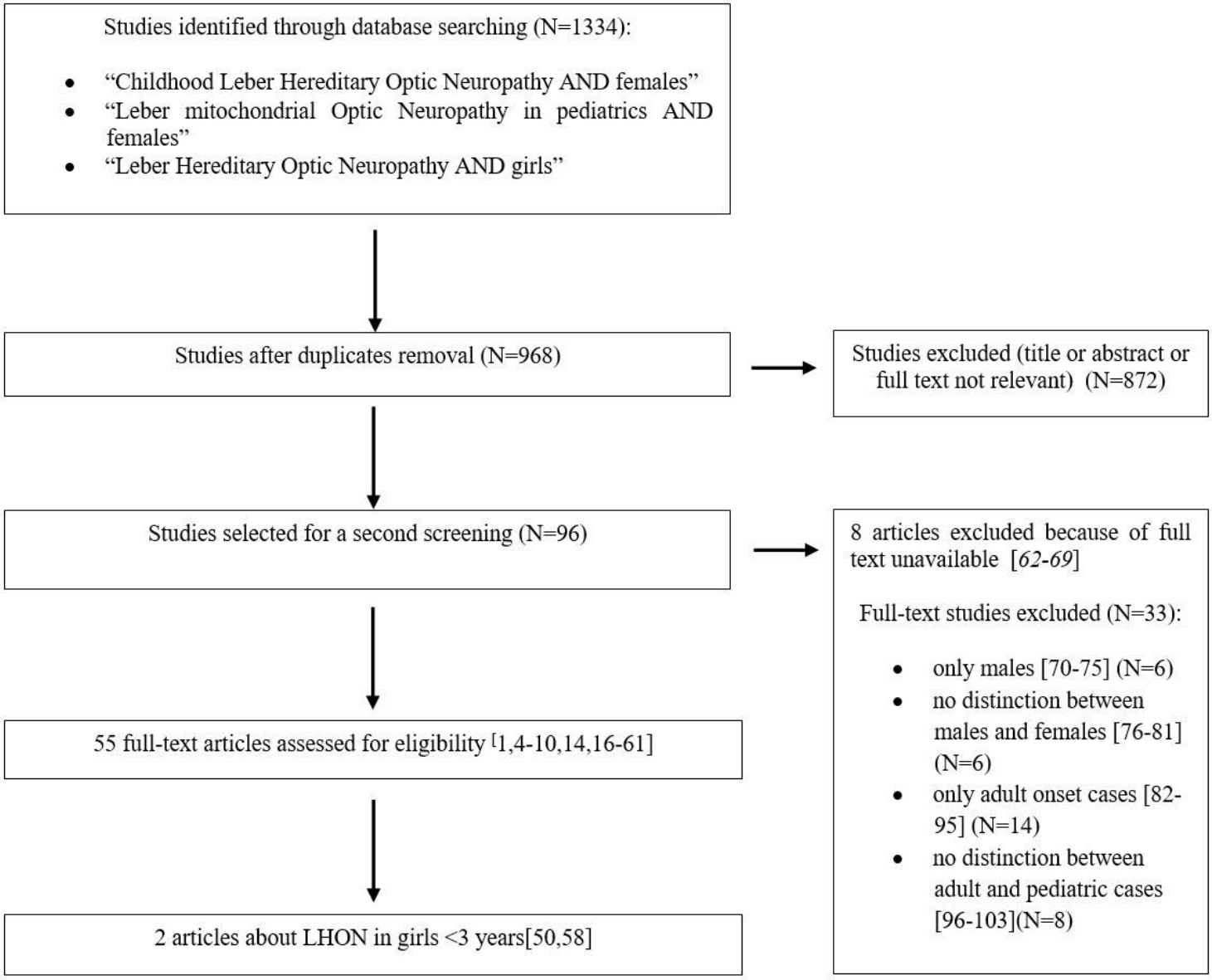

Figure 1

Literature search algorithm

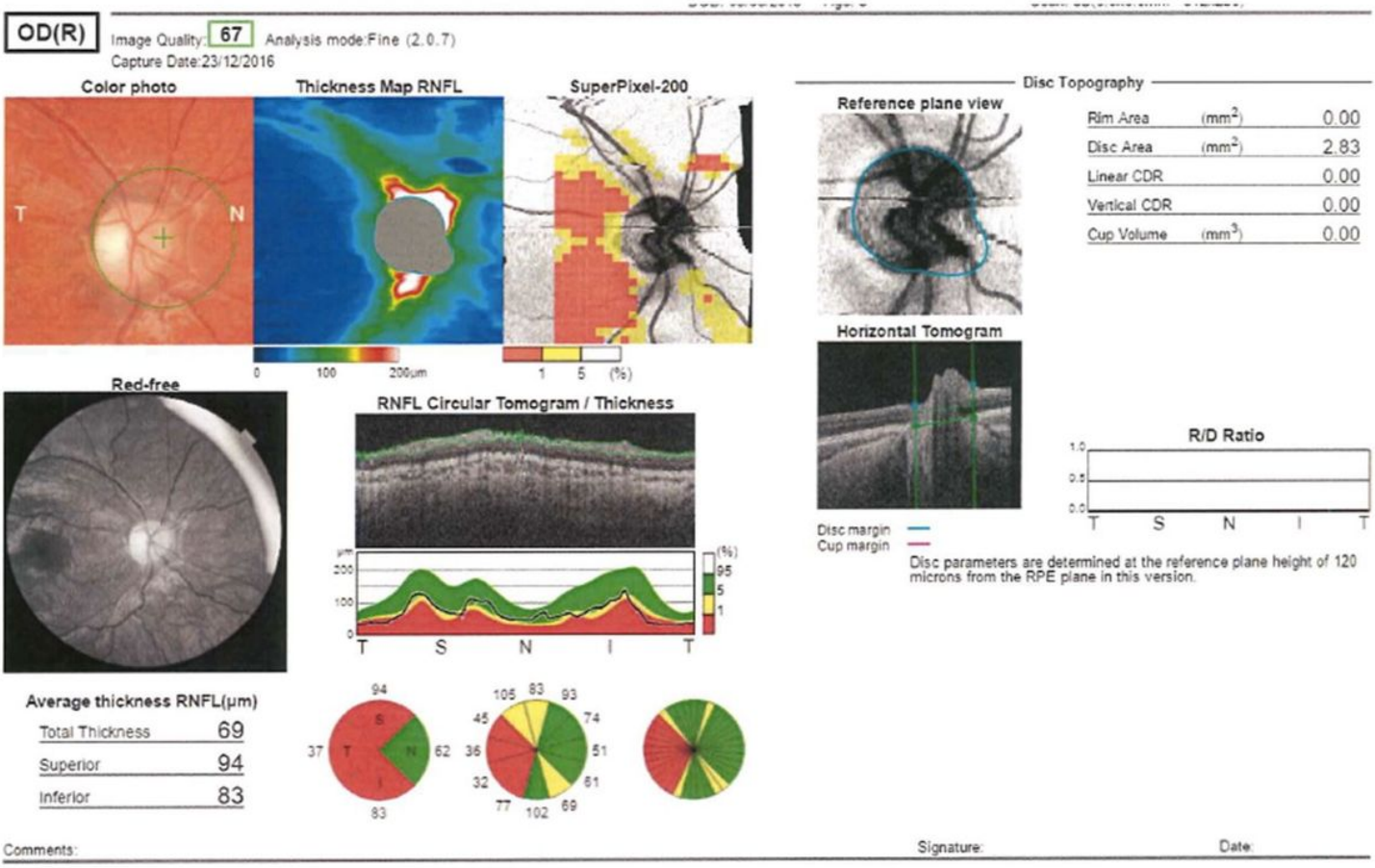

Figure 2

OCT at onset of LHON

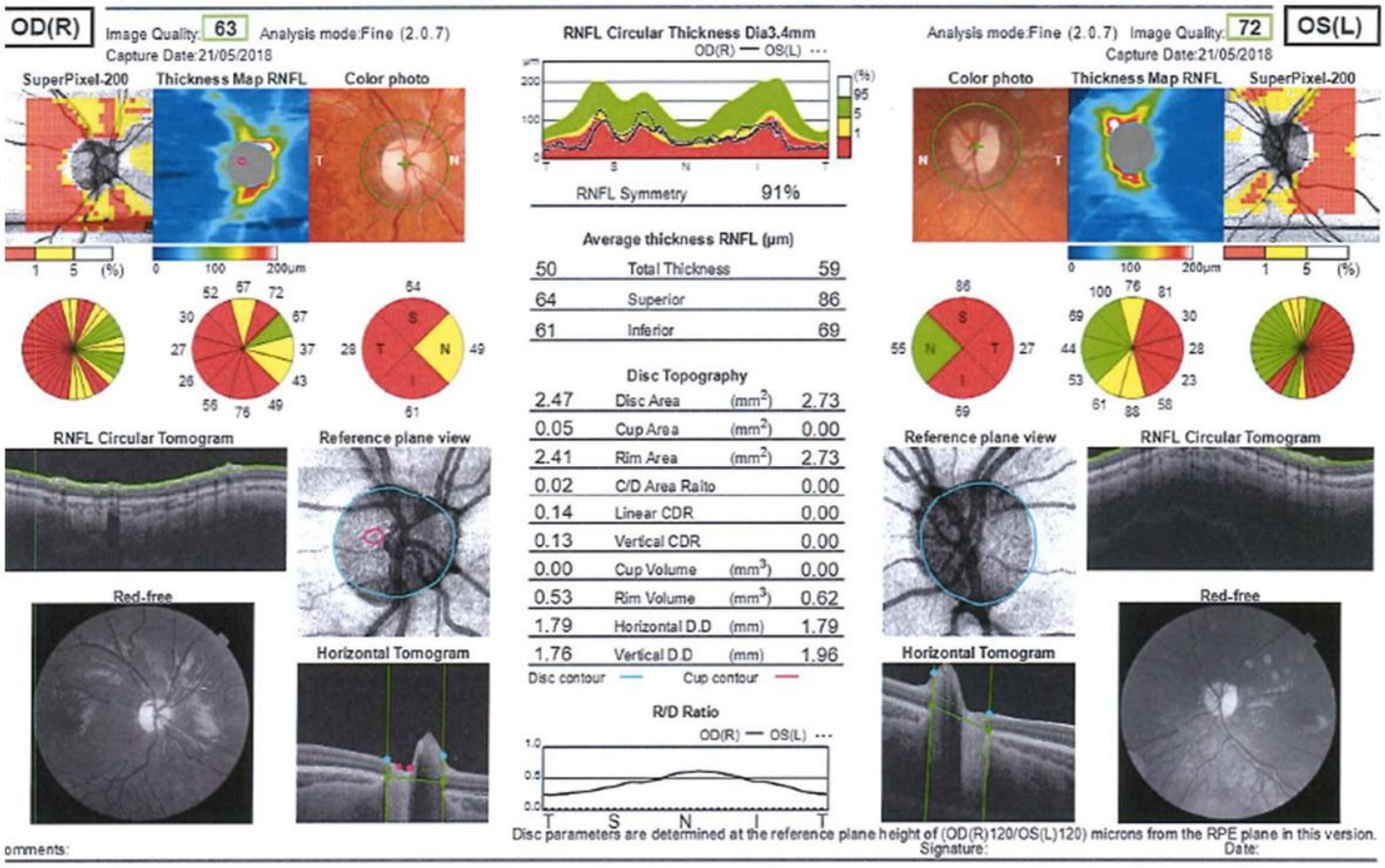

Figure 3

OCT at follow up three years after the onset

Figure 4

A drawing of self-perception by our child at the age of 5 years old