Case Report

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Leber Hereditary Optic Neuropathy (LHON) in Patients with Presumed Childhood Monocular Amblyopia

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Abstract: Background: Most of the Leber hereditary optic neuropathy (LHON) cases are bilateral and sequential, however there are rare unilateral examples, or those in which the delay of onset of vision loss between one and the other eye is longer. In the case of presumed childhood amblyopia in one eye, the vision loss in the good eye may be the only symptom of bilateral disease, that was unnoticed in previously amblyopic eye, or a preexisting episode of LHON on the "amblyopic" eye. Clinical decision in such cases may be difficult and suggestive for other forms of atypical optic neuropathy until confirmed by genetic testing. **Case series**: We present three genetically confirmed (MT-ND1:m.3700G>A, MT-ND6:m14484 T>C, and MT-ND4:m.11778G>A) patients with subacute vision loss in previously good eye with the other eye believed to be amblyopic from the childhood, and their features different of what would be expected in true amblyopia. In all, electrophysiology testing showed bilaterally reduced amplitude of PERG with low VEP P100 wave amplitudes and prolonged peak time in both eyes, also unusual for amblyopia. During the follow-up, pallor of the optic discs progressed in all eyes. Significant thinning of the retinal nerve fiber layer around the optic disc (pRNFL) and ganglion cell complex (GCC) in the macular region was present. All three patients had peculiar history. First patient was treated for presumed hyperopic amblyopia that did not improve since childhood and experienced visual loss on the good eye at the age of 17 and was negative for the three typical LHON mutations. Extended testing confirmed atypical pathogenic variant MT-ND1:m.3700G>A in homoplasmy. The second patient with presumed strabismic amblyopia had unusual presentation of vision loss only at the age of 61 and after exclusion of other causes, typical MT-ND4:m.11778G>A pathogenic variant was found in homoplasmy. The third case was peculiar as he had presumed strabismic amblyopia since childhood and had some degree of disc pallor in the amblyopic eye upon presenting with loss of vision on the good eye at the age of 21 and typical pathogenic variant m14484 T>C, p.Met64Val was subsequently confirmed. However, one year after the disease onset, he started to experience significant spontaneous functional improvement in the non-amblyopic up to 1.0 Snellen, whilst improvement in the presumed amblyopic eye was modest, suggesting preexisting amblyopia. This interestingly extensive improvement was carefully followed by electrophysiology as well as visual acuity and fields. **Conclusion:** This report shows three different scenarios of presentation of LHON in patients with presumed uniocular amblyopia from childhood. In such cases, the diagnosis may be difficult and detailed structural and functional evaluation of the optic nerve head is necessary to assess whether earlier LHON episode was misdiagnosed as amblyopia or whether LHON presented bilaterally on both eyes whilst only being noticed in the previously good eye.

Keywords: LHON; amblyopia; low visual acuity; retinal thickness; segmentation analysis; visual acuity improvement

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1. Introduction

Leber hereditary optic neuropathy (LHON) is a mitochondrial neurodegenerative disease characterized by painless, acute or subacute loss of the central visual acuity (VA). Disease usually affects both eyes, either simultaneously in 25% of patients, or sequentially within a few weeks or months [1]. However, individual unilateral cases [2–11] and cases with delayed onset between two eyes have also been reported [12]. 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 [4,10,13–20]. The atypical age of onset and clinical patterns of visual loss frequently result in significant diagnostic delays with possible initial misdiagnoses. Amblyopia is a visual disorder characterized by a subnormal visual acuity (VA) of different grades in one or both eyes, caused by either visual deprivation or abnormal binocular interactions with normal retinal and optic nerve structure [21].

In this paper, we present detailed phenotypes, and follow-up of the three genetically confirmed LHON patients with one eye believed to be amblyopic since childhood that presented with LHON in the good eye later in life.

2. Materials and Methods

Three patients who had poor visual acuity in one eye since childhood were selected from the cohort of genetically confirmed LHON patients at Eye Hospital, University Medical Centre Ljubljana. According to medical history data, low vision in one eye was identified already in childhood, years before the typical presentation of LHON on the other eye. Ophthalmological examinations were performed at the presentation as well as during follow-up periods and included: best-corrected visual acuity (Snellen chart, decimal notation), color vision (Ishihara plates), visual field examination (Goldman or Octopus perimetry), fluorescein angiography (FA), and electrophysiology testing. Visual acuities counting fingers and hand motion were expressed as decimal numbers [22,23] and converted to LogMAR using online calculator (https://www.myvisiontest.com). Ring analysis of the retinal nerve fiber layer around the optic disc (peripapillary retinal nerve fiber layer- pRNFL) was done with spectral domain optical coherence tomography (SD-OCT) and segmentation of the retinal layers was performed by the Spectralis HRA apparatus (Heidelberg Engineering, Heidelberg, Germany) in nine Early Treatment Diabetic Retinopathy Study (ETDRS) grid fields [24,25]. Electrophysiological testing with large-field pattern electroretinogram (PERG) and visual evoked potentials (VEP) were recorded with Espion visual electrophysiology testing system (Diagnosys LLC, Littleton, MA, USA). All electrophysiological tests followed the standards of the International society for Clinical Electrophysiology of Vision (ISCEV). The pathological variants in mtDNA were identified with Multiplex Ligation-dependent Probe Amplification (MLPA) and next-generation sequencing of the mtDNA.

Patients provided written informed consent according to regulations of University Medical Centre Ljubljana; the use of clinical data was approved by the National Committee for Medical Ethics (No:0120-626/2019/5, date: 17/3/2020).

3. Results

Presented is a case series (3 patients) with LHON and a likely past history of amblyopia during childhood and who later developed LHON on the good eye, whilst the changes in amblyopic eye were subjectively unnoticed.

3.1. Patient 1 (MT-ND1:m.3700G>A)

Patient 1 was a male patient of Slovenian origin, who suffered from a sudden VA decline in the left eye (LE) at the age of 17. Detailed medical history and disease progression is presented in Supplementary Table S1. As a 6-year-old child, he had been first seen at the Eye hospital due to low vision in one eye (RE: 0.1 cc, LE:0.7c.c). Hyperopic glasses (+7.0 Dsph and +6.5 Dsph) were prescribed and VA improved on both eyes to RE: 0.3 c.c. and LE: 1.0 c.c. Amblyopia treatment with the occlusion

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of the LE was started, but the vision of the RE did not further improve despite occlusion therapy. However, in absence of other clinical signs, no additional diagnostic workup was performed at that time.

3.1.1. Disease Onset

The patient was referred to the Eye hospital 5 months after the insidious onset of gradual visual decline on the LE at the age of 17. On admission, the RE VA was counting fingers at 2 meters (3pprox.. 0.03, 1.52 LogMAR) and LE counting fingers at 1 meter (3pprox.. 0.015 Snellen, 1.82 LogMAR). The patient did not subjectively notice any additional visual loss on the amblyopic eye. His refractometry at that time was RE: + 2,0 – 1,25/5 LE: + 1,5 – 1,75/180, eye movements were normal and painless with no squint.

Color vision was RE 0/15 and LE 1/15 and there was central scotoma in the visual field of both eyes (Figure 1). Both optic nerve heads (ONH) were mostly pink with some pallor in the temporal part, more on the amblyopic RE, while the blood vessels were slightly tortuous (Figure 1). The thinning of the pRNFL on OCT was present in temporal half of the optic discs, whilst nasal was still preserved. Electrophysiology showed reduced amplitudes of PERG N95 waves and reduced amplitude and the prolonged peak time of VEP P100 waves bilaterally, more in the presumed amblyopic RE (Supplementary Table S2). A rare, previously published MT-ND1:m.3700G>A pathogenic variant in homoplasmy was confirmed. His sister and mother were asymptomatic carriers of the same variant.

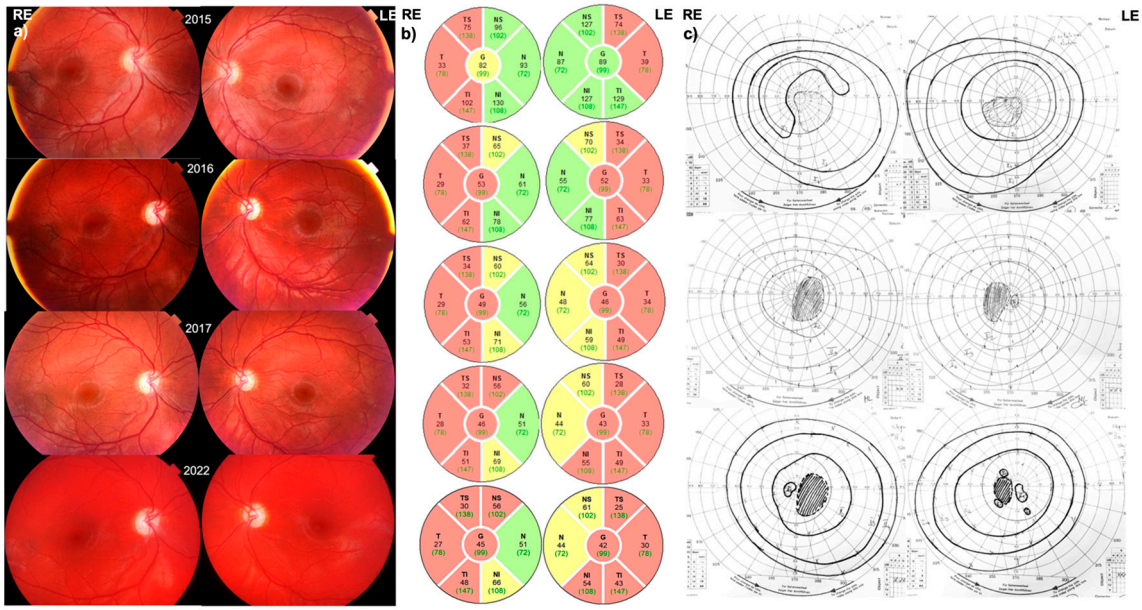

Figure 1. a) Fundoscopy, b) peripapillary RNFL and c) visual field of Patient 1 at presentation and during the 7-year follow-up period. Note the development of disc pallor in both eyes on the fundoscopy with progressive thinning of pRNFL (marked with red) and persistent central scotoma. Green fields represent parts that still have normal or thickness greater than normal, yellow fields have a borderline thickness and red fields mark thickness less than normal (atrophy of the peripapillary RNFL).

3.1.2. Follow-Up

During the follow-up, his VA did not improve, and disc pallor progressed bilaterally with thinning of the RNFL layer. Segmentation analysis of the retinal layer thickness showed thinning of the GCC in all ETDRS segments in both eyes which stabilized in the last years of the follow-up (Supplementary Table S3). Electrophysiology tests showed VEP P100 wave was undetectable, and the PERG N95 wave reduced to the level of the baseline in both eyes.

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3.2. Patient 2 (MT-ND4:m.11778G>A)

Patient 2 was a 61-year-old male of Serbian origin at the time of the decline in VA in his left, previously normal eye in January 2017. He also did not subjectively notice vision loss in the amblyopic eye. Detailed medical history and disease progression is presented in Supplementary Table S4. He had low vision in his right eye since early childhood, presumably due to a strabismic amblyopia and he remembered that he had squint surgery.

3.2.1. Disease Onset

At the time of the examination, (two weeks after the visual loss in his previously good LE) VA was counting fingers at 2 meters (approx. 0.03, 1.52 LogMAR) bilaterally, color vision in both eyes was 1/15, there was a bilateral loss of the entire visual field with some remaining islands of vision seen by searching, with bilateral hyperemic ONH with tortuous blood vessels, typical for acute stage of LHON. Peripapillary RNFL was swollen and thicker than normal, slightly more in the temporal region of the amblyopic RE in comparison to the LE (Figure 2). Fluorescein angiography showed no leakage. His refraction was RE:+ 2,0 + 0,75/160; LE:+ 2,0 Dsph, the eye movements were normal and painless, without squint.

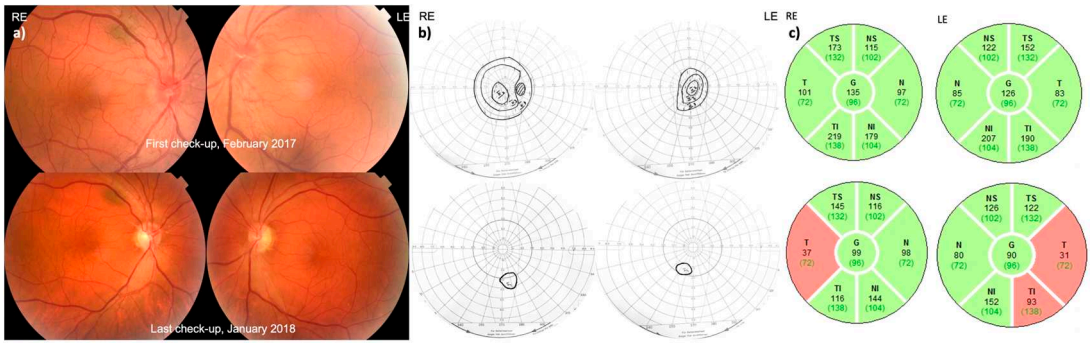

Figure 2. a) Fundoscopy, b) visual field and c) peripapillary RNFL of the Patient 2 at the first visit and at the follow-up one year later. Note pseudoedema of both discs upon onset and temporal pallor and RNFL thinning at the last visit on fundoscopy.

3.2.2. Follow-Up

Six months after the loss of vision in the LE, electrophysiology showed decreased amplitude of the PERG N95, and undetectable VEP P100 on both eyes (Supplementary Table S2). Thinning of the pRNFL in the temporal region on both eyes was seen, more prominent on the previously good left eye. Nine months after the onset, there was still preservation of the pRNFL on the presumably amblyopic eye in N, NS, NI, and TS region, whilst on the LE, the pRNFL was preserved only in N and NI segment. One year after the onset complete atrophy of the pRNFL was present in both eyes (Figure 2). The thinning of ganglion cell complex (GCC) was also seen on the segmentation analysis of both eyes (Supplementary Table S3). The pathogenic variant MT-ND4:m.11778G>A, homoplasmy, was then confirmed in the patient. Based on the family history, the patient's mother also suffered from bilateral VA loss at an older age due to optic neuropathy. This patient moved out of the country and was later lost to follow-up.

3.3. Patient 3 (m14484 T>C, p.Met64Val)

Patient 3 was a 21-year-old male of Albanian origin from Kosovo who noted gradual painless loss of visual acuity in his RE over a period of 2-3 weeks. He had poor acuity in the left eye since childhood presumed due to amblyopia with severe convergent strabismus (Supplementary Table S5). Two uncles on the mother's side of the family apparently had a similar episode of vision loss and then improvement at a younger age.

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3.3.1. Disease Onset

On admission, three weeks after the onset, VA in the previously normal RE was counting fingers at 3 m (approx. 0.05 decimal, 1.30 LogMAR), while in the left, presumably amblyopic eye, it was counting fingers at 2.5 m (approx. 0.04 decimal, 1.40 LogMAR). Loss of vision was subjectively noticed only on previously good right eye. Color vision was 1/15 in both eyes. Static perimetry showed central and inferior scotoma on the LE and small central scotoma with additional concentric loss of sensitivity on the LE (Figure 3). Both discs were temporally paler, more on the amblyopic eye, with no signs of acute hyperemia.

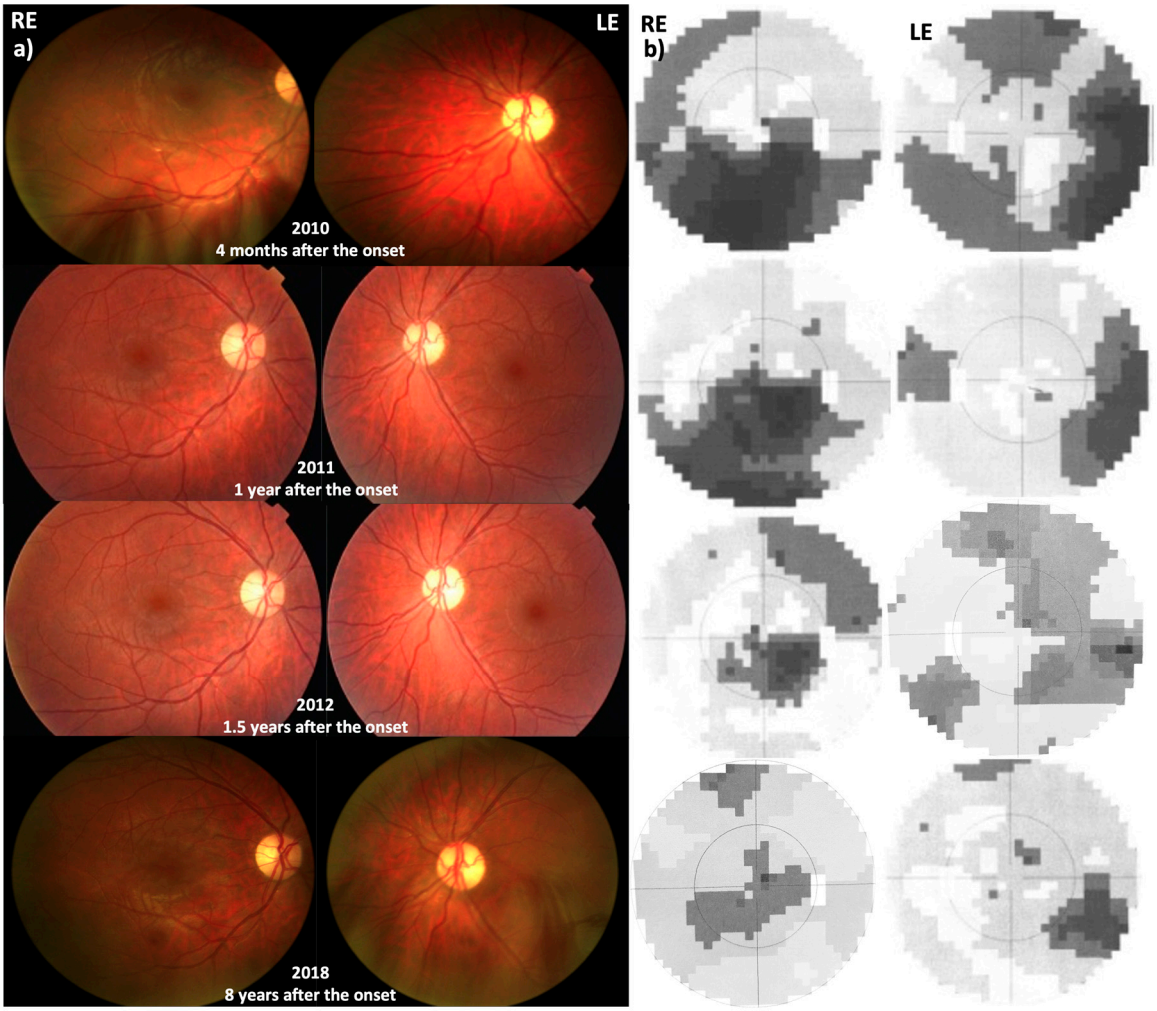

Figure 3. a) Fundoscopy results during the follow-up with the pallor of the optic discs. b) Visual fields during the follow-up. Note gradual improvement of the visual field over time despite paler discs.

There was no leakage on fluorescein angiography on either eye. Pattern ERG N95 wave were decreased, and VEP P100 were decreased and delayed from both eyes, more on the amblyopic eye.

Genetic testing confirmed the typical MT-ND6 pathogenic variant: m14484 T>C, p.Met64Val (homoplasmy).

3.3.2. Follow-Up

Four months after the onset VA was bilaterally 0.1 decimal (1.0 LogMAR) and Ishihara 1/15. Microperimetry, performed 6 months after onset, showed reduced central sensitivity on the RE and extremely eccentric fixation on presumably amblyopic LE. Electrophysiology signals were reduced accordingly (Figure 4). One year after onset, bilateral VA was still 0.1 decimal, Ishihara still 1/15, discs were paler than earlier on both eyes (Figure 3).

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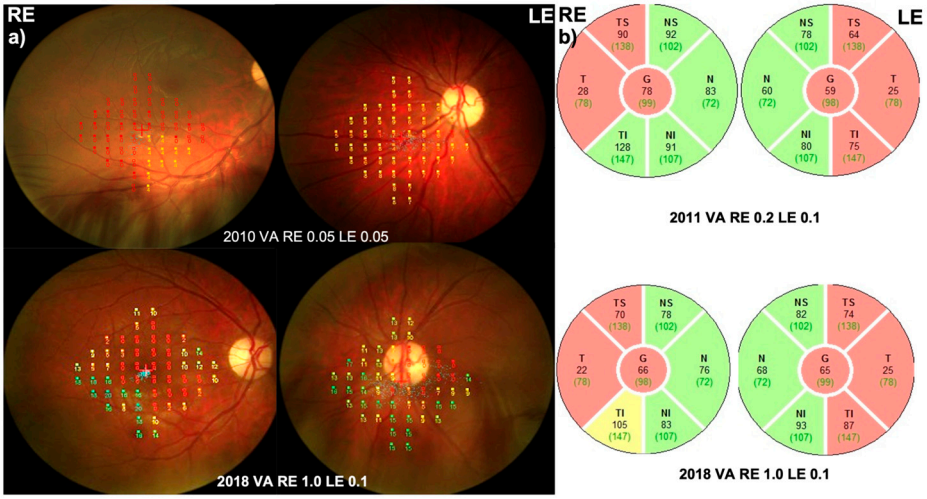

Figure 4. a) Microperimetry and b) pRNFL in Patient 3 at onset and during the follow-up period. Note good functional improvement on the right eye and, to some extent, on the left amblyopic eye by microperimetry. Despite functional improvement, the thickness of the pRNFL continued to decline slightly during the follow-up period.

Interestingly, one and a half years after the disease onset VA started to improve (RE 0.2, LE 0.1), and continued to improve to reach 0.8 in the RE two years after the disease onset. Color vision improved slightly from 1/15 to 3/15.

Six years later, eight years after the onset, at the age of 29, the RE VA improved even to 1.0 Snellen and color vision improved to 6/15, with fenestration of visual field scotoma and improvement of light sensitivity on microperimetry. VA and color vision on amblyopic LE did not improve substantially (0.1 Snellen, 1/15 Ishihara). Slight improvement was noted on microperimetry also in the amblyopic eye but was not subjectively perceived (Figure 4).

3.4. Segmentation Analysis and pRNFL

In all eyes of Patients 1-3, segmentation analysis of retinal layers showed significant thinning of GCC in all other segments (Supplementary Table S3) with discrete preservation of GCC in the central ETDRS field. The amblyopic eyes had an overall thicker retina and GCC in the central ETDRS circle compared to subacutely affected eyes. No differences were observed in other ETDRS rings or for other retinal layers between amblyopic and subacutely affected eyes (Supplementary Figure S1). The peripapillary RNFL showed a continued trend of atrophy in both the presumed amblyopic eye and the previously good eye (Supplementary Figures S2–S4) both in the nasal and temporal segments. In the Patient 3, who has improved on the good eye, pattern of GCC thinning showed progressive decline at the disease onset and later stabilization during the follow-up in both, the good and presumably amblyopic eye (Supplementary Table S3). Improvement of visual acuity was not associated with thickness change.

We describe three patients with monocular low vision in one eye since early childhood, believed to be due to amblyopia, that presented many years after with subacute vision loss on the previously good eye. The question arises whether low vision on the first eye was actually due to an early LHON episode, or was there indeed true amblyopia at that time, with superimposed LHON affecting both eyes later in life, especially as none of the patients reported any loss or change of vision in their amblyopic eye. In the presented patients, unfortunately, no report on optic disc pallor was available in their childhood notes and no OCT or other imaging was available at that time. Patients 1 and 3 already had some pallor of the ONH in the amblyopic eye at the time of the LHON episode in the previously healthy eye. This is an unusual finding in amblyopia and may suggest earlier episode of LHON. Their different scenarios were therefore clinically challenging and was the reason for detailed morphological and functional follow-up described in this paper.

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Patient 1 lost vision on the good eye at the age of 17 and there was no strabismus, anisometropia or media opacities or other amblyogenic factors present. Testing for three common genetic pathological variants of LHON was negative. Extended mitochondrial genome testing revealed rare, previously published [26]. MT-ND1:m.3700G>A pathogenic variant in homoplasmy. As on presentation, partial disc pallor was already present on amblyopic eye it may be possible that LHON affected the amblyopic eye earlier. However, it is not possible to determine whether LHON was already the cause of "amblyopia". with insidious onset in childhood or whether the true amblyopic eye was additionally affected in subacute fashion later, that remained unnoticed due to poor vision until the good eye was affected. As he had a slight progression of the pRNFL thinning during the disease course and electrophysiology typical for LHON on both eyes, he may correspond to bilateral sequential onset which had initially started on the amblyopic eye, however, is also possible that it could have been caused by a childhood-onset LHON since the patient did not respond to standard amblyopia treatment.

Three different patterns of visual acuity loss were described in childhood LHON: Classical acute in 63%, slowly progressive in 15%, and insidious or subclinical in 22% [10]. Recent paper by Barboni et al. [11] proposed a different classification of childhood-onset LHON: Subacute bilateral (66.7%), insidious bilateral (17.3%), unilateral (11.1%), and subclinical bilateral (4.9%). According to these studies, different patterns could affect either eye. The specific pattern of insidious unilateral onset in early infancy is quite peculiar, and asymmetric involvement may arise as a consequence of the subtle anatomical differences between the eyes, 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 the eyes [27,28]. In our patient, OCT showed some advancement of atrophy during follow-up also on the amblyopic eye which could suggest insidious onset and slowly progressive pattern.

Patient 2 showed characteristic ONH hyperemia, tortuosity of blood vessels, and pseudoedema simultaneously in both eyes although no additional worsening of vision was noted on the previously amblyopic eye. This patient remembered strabismus management with surgery in childhood, in keeping with true strabismic amblyopia. Clinically, this patient had a bilateral symmetric onset of LHON at the rather advanced age of 61, and symmetrical pseudoedema with atypical visual field loss prompted diagnostics towards other neurological causes until genetic testing confirmed the diagnosis.

In Patient 3, the affected eye developed convergent strabismus and could therefore be associated with strabismic amblyopia, however, strabismus can also develop secondary to visual loss due to LHON or any other cause [29]. Partial ONH atrophy was probably present before the second eye was affected since changes in the visual field and color vision were already noted at the first presentation in the absence of acute signs of disease. It is possible that the first attack could have occurred before the age of five (convergent strabismus usually occurs if the visual acuity in one eye is low before the age of five, while divergent strabismus develops at a later age) [29].

In the case of Patient 3 the most probable scenario is insidious unilateral LHON with consequential development of strabismus. Strabismus has been reported in cases of the unilateral childhood LHON and is usually associated with low visual function [4,12]. Barboni et al. reported strabismus in all patients with unilateral LHON [11]. They also described the subgroup of patients with the involvement of the second eye at the later age (≥15 years old) which could correspond to our Patient 1. In insidious unilateral patient group the younger presumed age of onset and the presence of strabismus could influence the final visual outcome due to a mechanism of cerebral suppression [30,31].

Electrophysiology was characteristic for LHON in both eyes of all three patients, confirming LHON event at some point. If the fixation is normal, the PERG N95 in amblyopic patients is usually normal [32], whilst in all three patients, the PERG N95 wave was abnormal to similar extent. In all patients, VEP was also abnormal on both presumably amblyopic and LHON eye. This confirms that the disease on the presumably amblyopic happened prior or at the disease onset on the LHON eye.

All our patients also had low color vision both in LHON and presumably amblyopic eye. In patient with VA improvement, color vision on the presumably amblyopic eye also did not improve.

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This corroborates with LHON event in both eyes as color vision is not significantly reduced in amblyopia [33], with some alteration in color perception [34].

With regards to OCT characteristics either no differences were reported in pRNFL and macular thickness between amblyopic and non-amblyopic eyes [35], or significantly thicker RNFL was reported in amblyopic eyes [36]. Moreover, thicker retina in ETDRS center and thinner in the inner and outer ETDRS ring was observed in amblyopic compared to normal eyes [37], Although in our case series, all eyes were affected and this comparison is not valid, we also noted thicker GCC in the ETDRS center in amblyopic eyes than in subacutely affected eyes (Supplementary Figure S1 and Supplementary Table S5). Also, all eyes showed the pattern of better preserved GCC thickness in the central ETDRS field than paracentral ones, as described recently, suggesting that both eyes were also affected by LHON [38].

Taking into account everything above, it is most likely that Patients 1 and 3 in this case series suffered from a LHON episode in the presumed amblyopic eye earlier in life but had only noticed unilateral visual loss upon visual loss in the other eye. In Patient 2, the clinical picture was suggestive of severe bilateral subacute LHON although noted only at the previously good eye.

Delayed involvement of the second eye has been described as rare in adult-onset LHON (37–40). Despite the fact that 97% of LHON patients suffer from the involvement of the other eye within one year [2,4], there are a few reports of unilateral or delayed presentation of LHON. Two studies document unilateral vision loss with subsequent visual recovery in the affected eye [3,4]. Several reports describe a delay in fellow eye involvement for 3–8 years follow-up period [5,6]. Other reports document cases of unilateral involvement with a follow-up period of 18 months [7], 10 years [8], and 16 years [9]. The longest interval reported in the literature was 18-year difference in disease onset (at the age of 5) between the two eyes [12]. This time difference between the involvement of the two eyes could be explained by the possible presence of a larger number of mutated mtDNA in one optic nerve or the fact that mitochondrial expression in the other eye is increased after the attack on the first eye, compensating the energy defect [12].

5. Conclusions

When faced with acute loss of vision in the good eye associated with presumed amblyopia on the other eye, especially in the presence of optic atrophy or disc swelling in that eye, we should not rule out the possibility of LHON that occurred either in early childhood as the cause of low vision or was superimposed onto true amblyopia later in life and only became manifest upon involvement of the good eye. This report shows the importance of detailed structural ONH evaluation with OCT, visual field and color vision in any patient with amblyopia not responding to treatment.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Figure S1. Retinal and GCC thickness in central ETDRS circle in presumably amblyopic and LHON eyes; Figure S2. Peripapillary RNFL changes in the nasal and temporal half of the optic disc in patient 1; Figure S3. Peripapillary RNFL changes in the nasal and temporal half of the optic disc in patient 2; Figure S4. Peripapillary RNFL changes in the nasal and temporal half of the optic disc in patient 3; Table S1. Timeline of the disease progression in Patient 1; Table S2. Electrophysiology data for three patients on both eyes (LHON and presumably amblyopic) in the acute (three patients) and chronic (two patients) phase of the disease; Table S3 Supplementary Table S3 Difference in retinal thickness in presumably amblyopic and LHON eye in center, middle, and outer ETDRS ring for all patients; Table S4. Timeline of the disease progression in Patient 2; Table S5. Timeline of the disease progression in Patient 3.

Author Contributions: Conceptualization, M.H. , S.P.P, M.J.V.; methodology, M.H., M.J.V., M.S.H.; validation, M.H., ; formal analysis, S.P.P.; investigation, S.P.P., A.F., M.J.V., M.S.H. ; resources S.P.P., A.F., M.J.V; project administration M.H., data curation, S.P.P; writing—original draft preparation, S.P.P; writing—review and editing, S.P.P., M.H., M.J.V., A.F., M.S.H.; supervision, M.H.; funding acquisition, M.H. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the National Medical Ethics Committee of Slovenia (No:0120-626/2019/5, date: 17/3/2020). They received all examinations and procedures within full national insurance scheme.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study according to the regulations of University Medical Centre Ljubljana. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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