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Leber's hereditary optic neuropathy – a review and prevalence analysis in the Slovenian population

Leberjeva hereditarna optična nevropatija – pregled bolezni z analizo prisotnosti v Sloveniji

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Abstract

Leber's hereditary optic neuropathy (LHON) is a rare genetic mitochondrial disorder that causes blindness in young adults. Typically, it presents with a subacute, painless loss of vision in one eye, followed by the involvement of the other eye in a few weeks to months. It usually leaves permanent visual disability; rarely, partial spontaneous recovery of visual function is possible in some patients. The male to female ratio is estimated at 3:1. In recent years, the drug idebenone was registered for supportive pharmacological treatment possibly leading to partial vision improvement. Due to its rare nature, the disorder often remains misdiagnosed or undiagnosed. In this article, we present four clinical cases which, after an extensive and long-lasting diagnostics, unveiled themselves as LHON. In the Slovenian database of rare eye disorders that has been kept since 1996, the prevalence of LHON is 1/72000. When suspected, the family history of poor eyesight in the maternal line, genetic testing, and referral to a tertiary institution are crucial for confirmation and treatment.

Izvleček

Leberjeva hereditarna optična nevropatija (LHON) je redka dedna mitohondrijska bolezen, ki povzroča slepoto najpogosteje pri mladih odraslih. Navadno se izrazi kot subakutna, neboleča izguba vida na eno oko, ki ji sledi poslabšanje vida drugega očesa v nekaj tednih do mesecih. Bolezen večinoma pušča trajne posledice, le pri nekaterih bolnikih lahko v redkih primerih pride do delnega spontanega izboljšanja vida. Razmerje med moškimi in ženskimi bolniki se ocenjuje na 3 : 1. V zadnjih letih je z razvojem zdravilne učinkovine idebenone možno podporno farmakološko zdravljenje, ki lahko prispeva k delnemu izboljšanju vidne funkcije. Bolezen zaradi svoje redkosti velikokrat ostane ne- ali napačno diagnosticirana. V

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članku predstavljamo štiri klinične primere bolnikov, pri katerih se je po obsežnem in dolgotrajnem diagnosticiranju izkazalo, da imajo LHON. Od leta 1996 se v Sloveniji vodi baza bolnikov z redkimi dednimi očesnimi boleznimi. Na tej podlagi je ocenjena prevalenca LHON 1/72.000. Ob sumu na bolezen so ključni družinska anamneza slabovidnosti po materini strani, genetsko testiranje in napotitev na obravnavo ter zdravljenje v terciarno ustanovo.

1 Introduction

Leber's hereditary optic neuropathy (LHON) is the most commonly inherited mitochondrial disease with an estimated prevalence of 1/32,000 to 1/65,000 (1). In more than 90% of cases, the disease is caused by a point mutation in mitochondrial DNA at one of the three typical sites. The G11778A mutation accounts for approximately 50–70% of cases, the G3460A mutation for 8–25%, and the T14484C mutation for 10–15% (2). All three mutations result in the malfunction of complex I of the mitochondrial respiratory chain in the retinal ganglion cells. The consequences are the insufficient supply of adenosine triphosphate (ATP), which is crucial for the normal functioning of cellular mechanisms, and at the same time, elevated levels of oxidative stress. Due to the synergistic effect of the two pathophysiological processes, which are directly related to each other, gradual apoptosis follows, which is expressed in the eye as ganglion cell deterioration and thus atrophy of the optic nerve. This leads to a rapid decline of vision, which progresses to an almost complete loss of central vision (3,4). Other genetic, hormonal, and environmental factors also have a significant influence on the occurrence of the disease. Known risk factors for the development of the disease are smoking and excessive alcohol consumption (5-7). The ratio between male and female patients is estimated at 3:1 (8). Some patients, particularly those with the T14484C mutation, may experience spontaneous partial improvement of vision even years after the onset of the disease (1).

In this article, the clinical characteristics of the disease and treatment options are presented, together with a prevalence analysis of the disease in the Slovenian population, and four clinical cases of patients treated at the Department of Ophthalmology in Ljubljana which, after a long-lasting diagnostic, were diagnosed with LHON.

2 Clinical picture

LHON is characterized by subacute, painless loss of vision in one eye with accompanying deterioration of vision in the other eye over several weeks. It can occur at any stage in life, most often in the second and third decades, and very rarely after the age of 50 (8,9).

LHON is chronologically divided into four phases. In the pre-symptomatic phase, abnormalities at the fundus can be observed, including peripapillary telangiectatic blood vessels, a variable degree of retinal nerve fibre layer edema, as well as changes in the electrophysiological parameters (Figure 1) (11,12).

In the subacute phase, which is defined as the first six months from the onset of symptoms, patients report a deterioration of visual acuity, colour vision impairment, especially in the red-green colour spectrum, a decrease in contrast sensitivity, and the initial appearance of central scotomas in the visual field of one eye. Similar symptoms appear in the other eye on average six to eight weeks later, with both eyes being affected within six months. A bilateral vision loss from the beginning is present in only about a quarter of cases (Figure 2A, 4A) (9,11).

The dynamic phase refers to the time between six months to one year from the onset of symptoms. This phase is characterized by a further deterioration of visual acuity to the level of counting fingers and an enlarging scotoma in the central part of the visual field. In the subacute and dynamic phase, tortuous vessels, peripapillary telangiectatic microangiopathy, pseudo papilledema, and increased retinal nerve fibre layer thickness are seen at the fundus of the eye (Figure 2B, 4A, 5, 6). It is often stated that pupillary responses are preserved, but this is only true if the pathological process occurs simultaneously in both eyes. If only one optic nerve is affected, a relative afferent pupillary defect (RAPD) is present. In 20–40% of cases, the optic disk may still look completely normal (9,13).

After the first year from the onset of symptoms, the chronic phase begins, which is characterized by a relatively stable loss of the central vision (centrocecal scotomas), thinning of the temporal part of the optic nerve, and the deterioration of the papillomacular nerve fibre bundle (Figure 2C, 4C-D) (9,13). In most patients, vision will not improve throughout their lives and, in accordance with the legal regulations, the patients meet the requirements to be certified as blind or sight impaired (14). In some patients, however, a spontaneous improvement of vision can be observed even several years after the onset of the disease, especially in carriers of the T14484C mutation (1). The improvement is not limited solely to visual acuity, but may also include the development of small pockets of normal vision (fenestrations) within the central scotoma and an improvement in colour perception (11). Positive predictive

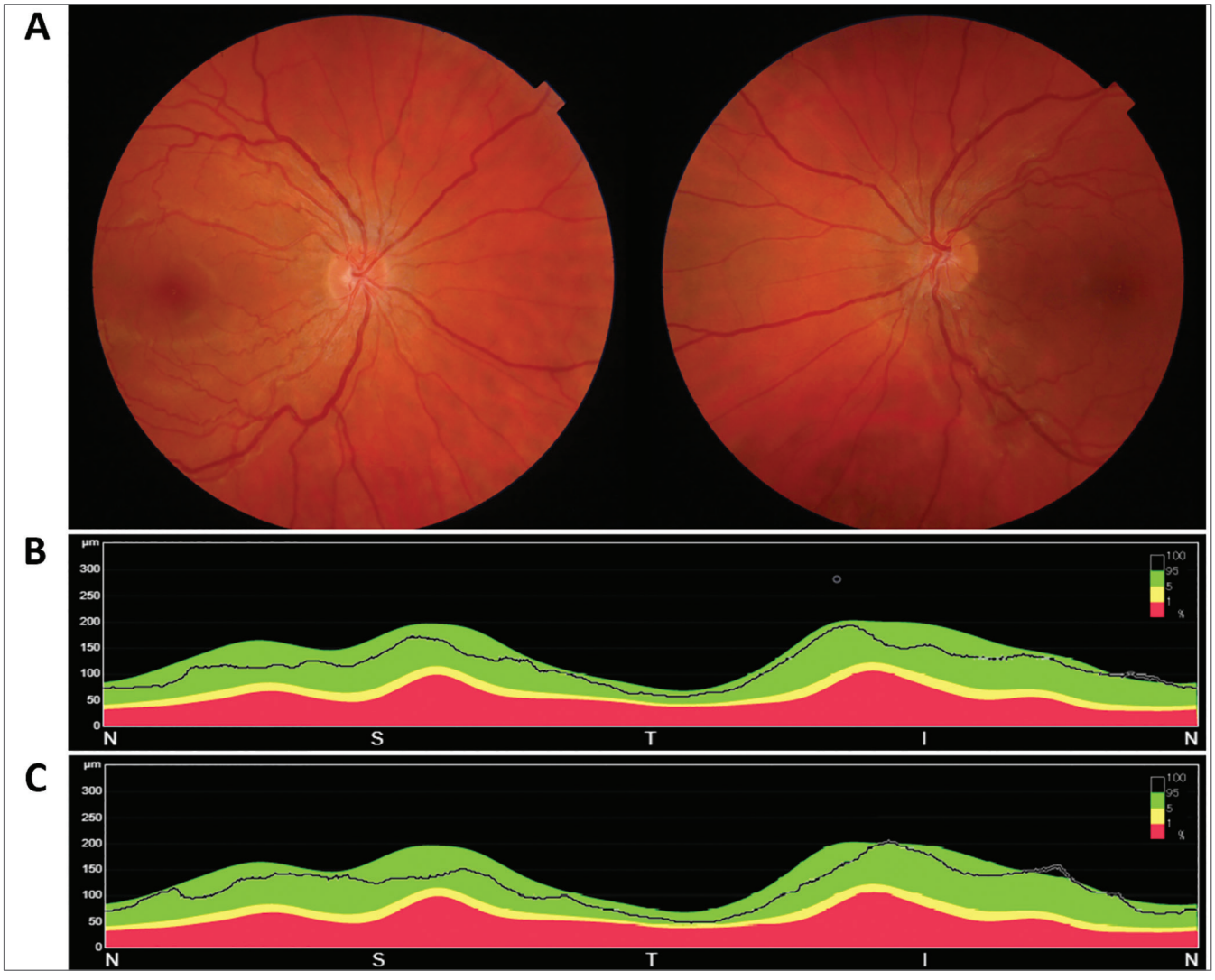

Figure 1: A patient without symptoms, carrier of the G3460A mutation (not described in the article) shows: A) the eye fundi with telangiectatic microangiopathy of the optic disks and tortuous vessels bilaterally, B) optical coherence tomography of the right optic disk, and C) optical coherence tomography of the left optic disk – preserved thickness of the peripapillary retinal nerve fibre layer across the entire diameter of both optic nerves.
The black line shows the mean thickness of the nerve fibres.
Legend: N – nasal; S – superior; T – temporal; I – inferior.

factors for visual improvement are early age (up to 20 years of age), subacute course with slow progression, genetic mutation type (T14484C), and large optic disk area (1,15,16).

In rare cases, extraocular manifestations may occur, including peripheral neuropathy, demyelinating disorders of the central nervous system, postural tremor, ataxia, myoclonus, myopathies, and cardiac rhythm disorders, which we describe as LHON plus syndrome, or Harding's disease (17-19).

3 Diagnostics

Due to its relatively rare nature, the path to a final diagnosis is often challenging and can take several years (10). A positive family history (loss of vision in the maternal line in several family members) is the most important factor for establishing a diagnosis, which leads us to suspect a genetic disorder (Figure 3). Diagnostics includes an ophthalmological examination (including evaluation of the visual acuity, colour vision, visual field, tonometry, and examination of the eye fundus), optical coherence tomography (OCT), electrophysiology, and laboratory and imaging tests. The clinical picture and test results depend on the stage of the disease (13). The final diagnosis is confirmed by genetic testing of a blood sample (9). Taking into account the current clinical state and the dynamics, many other diseases that may present themselves with a similar clinical picture have to be excluded in the process. By

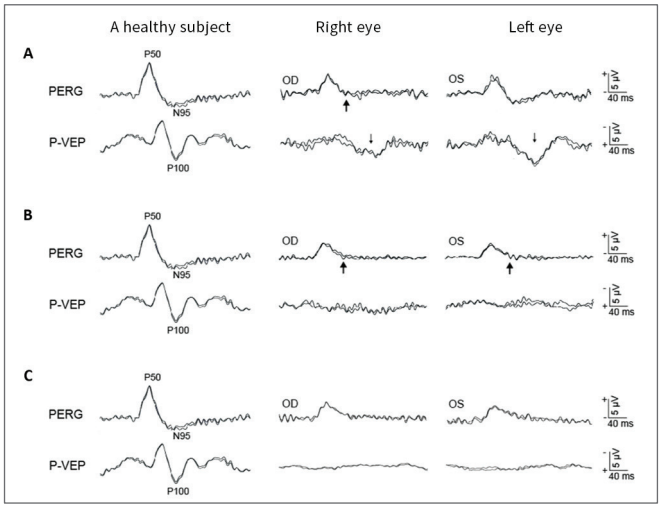

Figure 2: Electrophysiological changes in patients with Leber's hereditary optic neuropathy (not described in the article) according to the chronological course of the disease. A) in the subacute phase, B) in the dynamic phase, C) in the chronic phase.
A) in the subacute phase – two weeks after the onset of symptoms, the PERG N95 wave in the right eye is raised to the level of the isoline (indicated by a thick arrow), while remaining normal in the left eye. The VEP P100 wave is prolonged in both eyes (indicated by the narrow arrow) with reduced amplitude in the right. B) in the dynamic phase – five months later – both PERG N95 waves are abnormal (indicated by a thick arrow), as is the bilaterally not detectable P100 VEP wave. C) in the chronic phase – two and a half years after the onset of symptoms, the condition remains unchanged.
Legend: PERG – pattern electroretinography, VEP – visual evoked potentials. With permission from the authors (34).

examining the eye fundus and performing electrophysiological tests, retinopathy should be ruled out first (20). In a case of a rapid, gradual, painless deterioration of vision lasting from a few days to weeks, usually in the subacute and dynamic phase, optic neuritis or neuromyelitis optica (Devic's disease) is considered, and in a case of a bilateral involvement, toxic and nutritional optic neuropathy may be suspected. Normal-tension glaucoma, compressive and infiltrative optic neuropathy, and dominant optic atrophy should be excluded in a case of a slowly progressing disease or long-lasting poor vision (in the chronic phase) (13,21,22).

When treating patients, ophthalmologists must pay attention to the burdensome family history. Patients with bilateral vision loss that does not improve and those with an unexplained clinical picture should be referred to an appropriate tertiary institution for diagnostics and treatment when hereditary eye disease is suspected.

4 Treatment

In 2015, the European Medicines Agency approved the use of idebenone for the treatment of LHON (23). Idebenone is a synthetic ubiquinone analogue of coenzyme Q10 with pronounced strong antioxidant activity and improved pharmacokinetics. Due to its structure, it crosses the blood-brain barrier and the mitochondrial membrane more easily, where it transports electrons from the cytosol directly to the complex III of the respiratory chain,

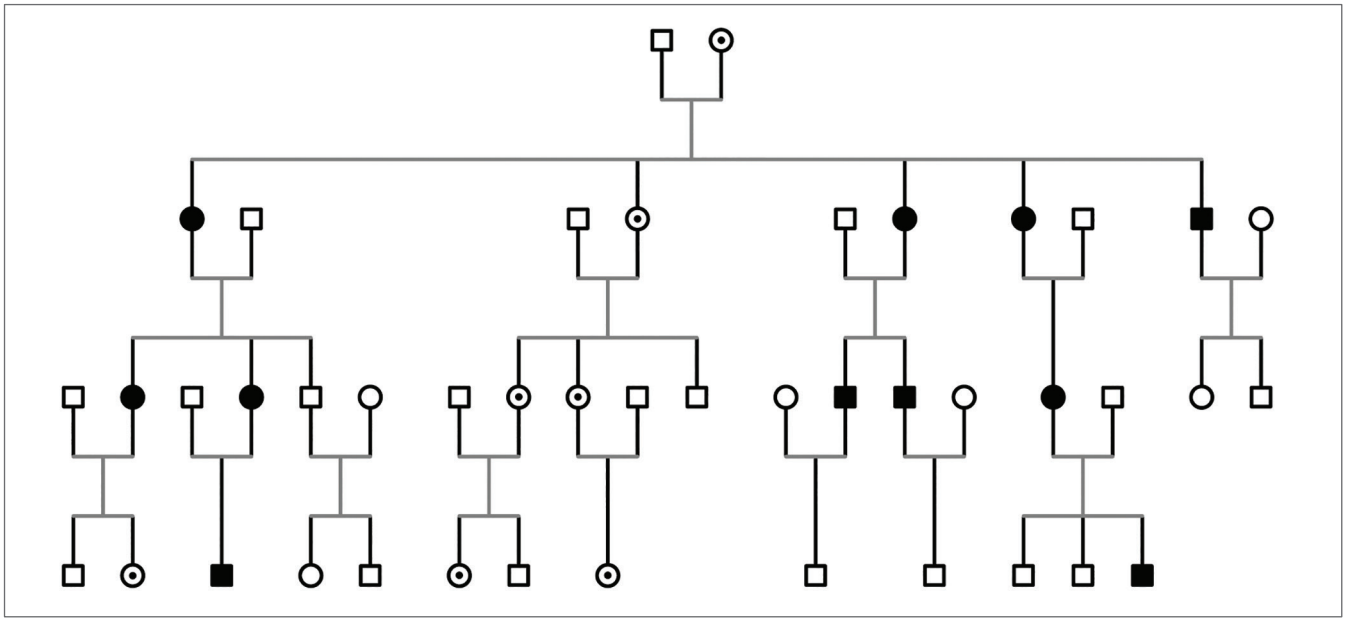

Figure 3: Pedigree of a family with Leber's hereditary optic neuropathy (not from the case described in the article).
A typical example of mitochondrial inheritance, in which a mother passes the mtDNA mutation to all her children. Fathers do not transmit mtDNA mutations to their offspring. Men are represented by squares and women by circles. A black filled symbol represents a patient with symptoms. A healthy carrier is marked with a black dot in a circle.

bypassing the inactive complex I and thereby improving ATP generation. In this way, it slows down or even halts the degeneration of retinal ganglion cells and reactivates still viable cells that have gone into a state of reduced activity due to the lack of ATP. This is mainly expressed as an improvement in visual acuity and a shortened time to the spontaneous improvement of vision (10,24). The most common side effects of idebenone treatment are an increased chance of nasopharyngitis, cough, and diarrhoea (23). The clinical efficacy of idebenone was tested in the randomized, double-blind, placebo-controlled RHODOS study on 85 patients who had lost their sight in the last five years before the study. Due to the inclusion criteria, which also included patients with advanced optic nerve atrophy and those with the T14484C mutation in which the proportion of spontaneous improvement is the highest, the authors of the study did not confirm the objectives of the primary observed event, i.e., the recovery of visual acuity. However, two years later the authors reported the durability of treatment effects in as many as 60 out of 85 patients (25). Based on the results of this study and additional retrospective analyses of 103 patients who received idebenone outside the study, the European Medicines Agency granted an exceptional use authorization in patients with LHON (26).

According to the current guidelines, treatment with idebenone should be initiated as soon as possible in patients who have had symptoms for less than a year. The drug should be taken in a dose of 900 mg/day, divided into three doses. The shortest period of treatment is one year. After one year, the response to treatment should be evaluated. According to some data, the response to treatment can last up to 30 months. If symptoms improve, the treatment should continue until a plateau is reached and extended for at least one more year. Despite some publications that report the effectiveness of the drug even in patients in the chronic phase, where symptoms had been expressed for more than a year with both eyes affected, there is still no expert consensus on this matter. There is also no expert consensus if asymptomatic carriers of the mutation benefit from prophylactic idebenone (13,21). In Slovenia, nine patients have received treatment with idebenone until 2021. Two patients completed the treatment.

With the advancement of biotechnology, the possibility of treatment with gene therapy has come to the forefront, which will probably pave the way for the treatment of many rare hereditary diseases in the future. Several possible therapies based on the use of adenoviral vectors are currently being tested. The goal of the therapy is to use an intravitreal approach to deliver a copy of a healthy gene to the nuclei of retinal ganglion cells, where it is preserved and leads to the production of a fully functional protein, which is then transferred to the mitochondria. Results from the recently published REVERSE and RESCUE studies in animals with the G11778A mutation provide encouraging results, as a clinically significant improvement, in at least one eye, was observed in 78% and 64% respectively, compared to the spontaneous expected improvement, which is estimated to be 4–33% with this mutation (27,28).

It is important that all patients with LHON are offered genetic counselling, especially the young and those in the acute phase. With prenatal diagnostics and the use of in vitro fertilization techniques, it is already possible to offer methods of reproduction (with or without the use of a donor egg) where the transmission of the disease to the offspring is to a certain extent prevented (29).

Table 1: The number of patients with Leber's hereditary optic neuropathy and their proportions according to gender and type of mutation in Slovenia.

LHON in Slovenian patients and their mutations	Number of patients	%
Demographics		
Men	16	59
Women	11	41
Typical mutations	20	74
G3460A (confirmed)	11 (5)	41 (18.5)
G11778A (confirmed)	9 (4)	33 (15)
Pathogenic variants	4	15
G13042T	2	7
A8381G	1	4
G3700A	1	4
Variants of uncertain significance (VUS); combinations of several variants	3	11
A3902G	3	
G3392C	1	
C3904A	1	
C12417A	1	
T15309C	1	

Values in parentheses represent the number and proportion of confirmed cases, the difference to the full value represents **the symptomatic cases that are still** in the diagnostic process.
Legend: LHON – Leber's hereditary optic neuropathy.

5 Leber's hereditary optic neuropathy in Slovenia

According to the database of rare hereditary eye diseases managed at the Department of Ophthalmology, University Medical Centre Ljubljana, a total of 16 cases of LHON had been confirmed from nine different Slovenian families (pedigrees) in Slovenia by 2021. The data are presented in Table 1.

The G11778A mutation is present in four patients, and the G3460A mutation in five. 11 symptomatic patients with an expressed clinical picture and a confirmed presence of LHON in the family are currently in the process of diagnostics; six patients come from a family with the G3460A mutation, and five patients from a family with the G11778A mutation.

In four patients, the presence of pathogenic variants G13042T, G3700A, and A8381G was confirmed, which are associated with the development of atypical LHON (30-32). In the remaining three with a clinical picture of LHON, the presence of variants A3902G, G3392C, C3904A, C12417A, and T15309C was confirmed in various combinations. These variants have not yet been recognized as potentially pathogenic and are so far considered as variants of uncertain significance (VUS).

The prevalence of LHON is estimated at 1/72,000, which is lower compared to the estimated prevalence in other European countries. It is a rough assessment, based on the data of already confirmed cases and expected confirmations in patients still in the diagnostic process. A meta-analysis of five epidemiological studies analysing prevalence data from northern England (1/32,000), the Netherlands (1/40–52,000), and Finland (1/50,000) estimates the prevalence of LHON in Europe for the three typical mutations at 1/45,000 (33). Currently, in Slovenia, new patients are still being discovered, which in the future will most likely lead to an increase in the prevalence of the disease.

The ratio between symptomatic men (16 patients) and women (11 patients) is estimated at 3:2, which can be explained by a relatively small sample, based on which we can only roughly estimate the state in the population. The predominant mutations are G3460A (41%) and G11778A (33%). A high proportion of pathogenic variants (15%) and variants of uncertain significance (11%) is also observed, while the T14484C mutation is not present at all. The distribution of the typical LHON mutations in the Slovenian population differs from the ones described in the literature of the Northern European countries. The presence of pathogenic variants together with variants of uncertain significance is 2.6 times higher in the Slovenian population due to the absence of the T14484C mutation, which is usually present in 10–15%, and the two-fold lower presence of the G11778A mutation, which is the most common in Europe with 50–70%. At the same time, the G3460A mutation is expressed

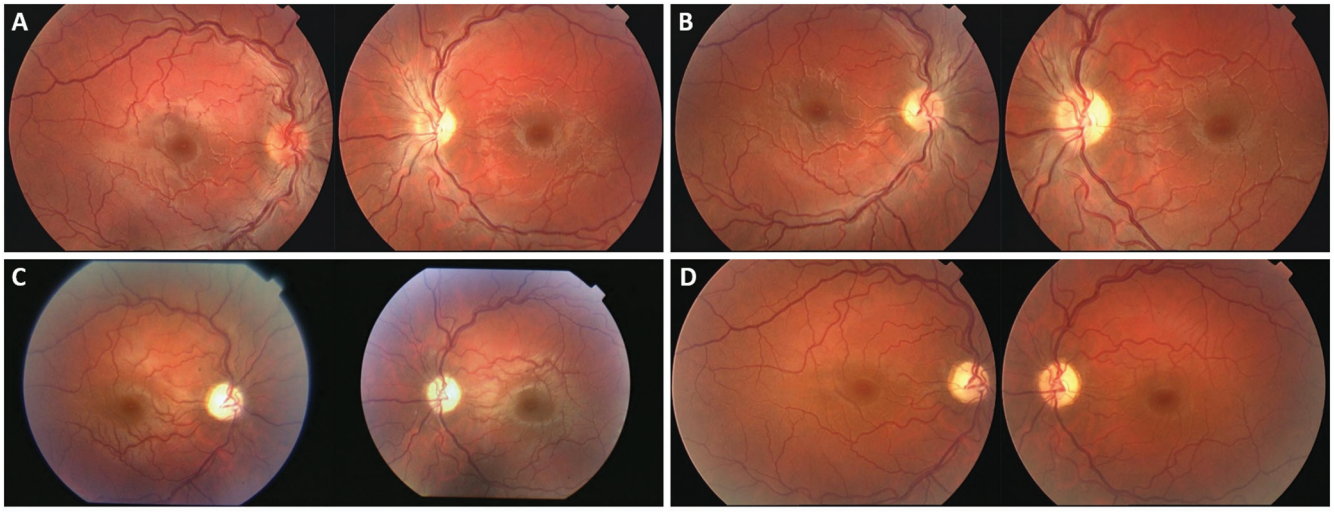

Figure 4: A clinical case; a typical presentation of a patient with Leber's hereditary optic neuropathy; shows the eye fundi of a patient with Leber's hereditary optic neuropathy at A) the first examination – on the right eye fundus, a hyperaemic optic disk, tortuous blood vessels, and pseudo papilledema are visible; on the left eye fundus, a pale, atrophic optic disk mainly on the temporal side is visible; B) after two months – noticeable reduction of pseudo papilledema on the right eye fundus, gradual pallor of the right optic disk, continuation of pallor and atrophy on the left eye fundus; C) after two years – marked pallor and atrophy of both optic disks; D) after five years – condition unchanged.

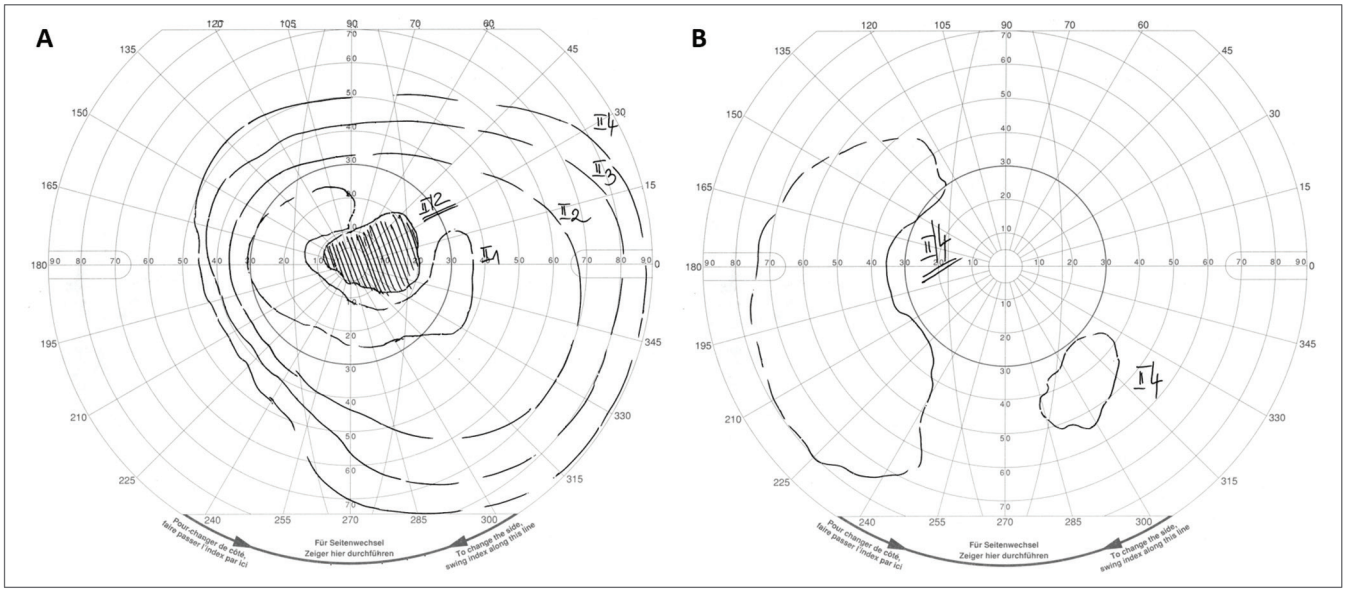

Figure 5: A clinical case; a typical presentation of a patient with Leber's hereditary optic neuropathy; shows Goldmann Visual Field at first examination (OD: 0.2 sc, OS: hand movement).
A) typical centrocecal scotoma in the right eye, B) complete central field defect in the visual field of the left eye.

2.5 times more than elsewhere in Europe (8–25%) (2). Differences in the distribution of the most common mutations could be attributed to the fact that rare pathogenic variants occur relatively more in smaller, more closed populations and in a smaller sample of patients. Two patients (7%) with simultaneously associated neurological symptoms have been diagnosed with LHON plus disorder.

6 Clinical cases

6.1 A typical presentation of a patient with Leber's hereditary optic neuropathy

Clinical Case: A 20-year-old man was treated at a regional hospital in July 2004 for sudden deterioration of

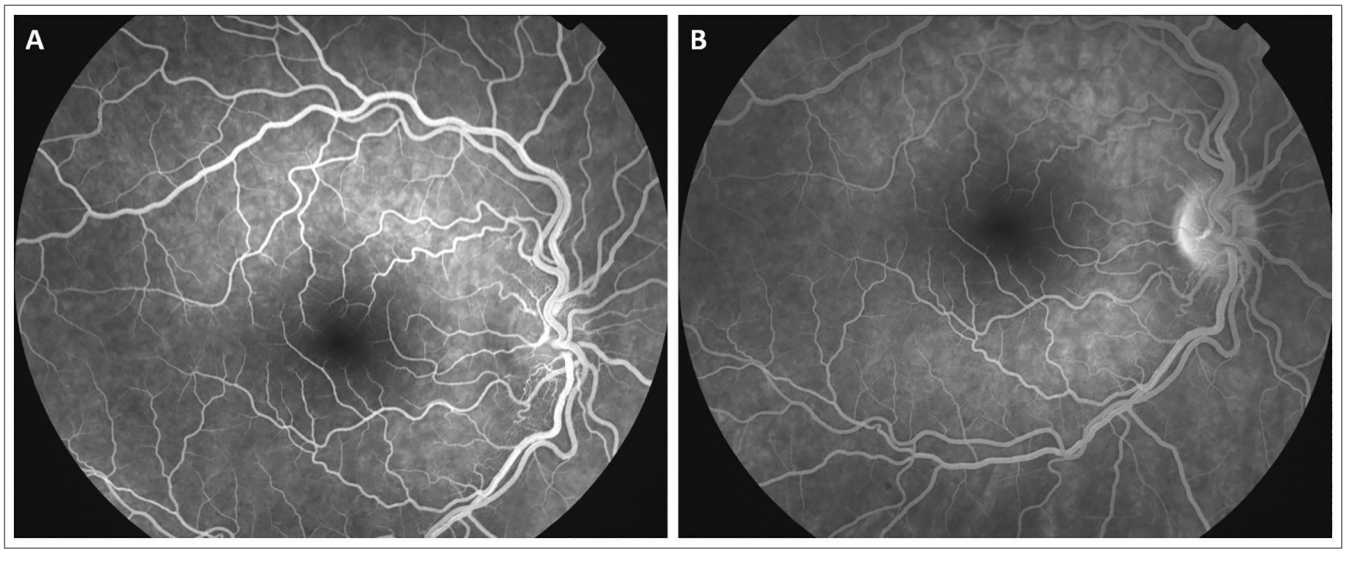

Figure 6: A clinical case; a typical presentation of a patient with Leber's hereditary optic neuropathy; shows the early (A) and late (B) phases of the fluorescein angiography in a patient with Leber's hereditary optic neuropathy.
In both images, we see markedly tortuous retinal blood vessels with hyperaemia of the optic disk, but without contrast leakage at the disk in the late stages of the examination.

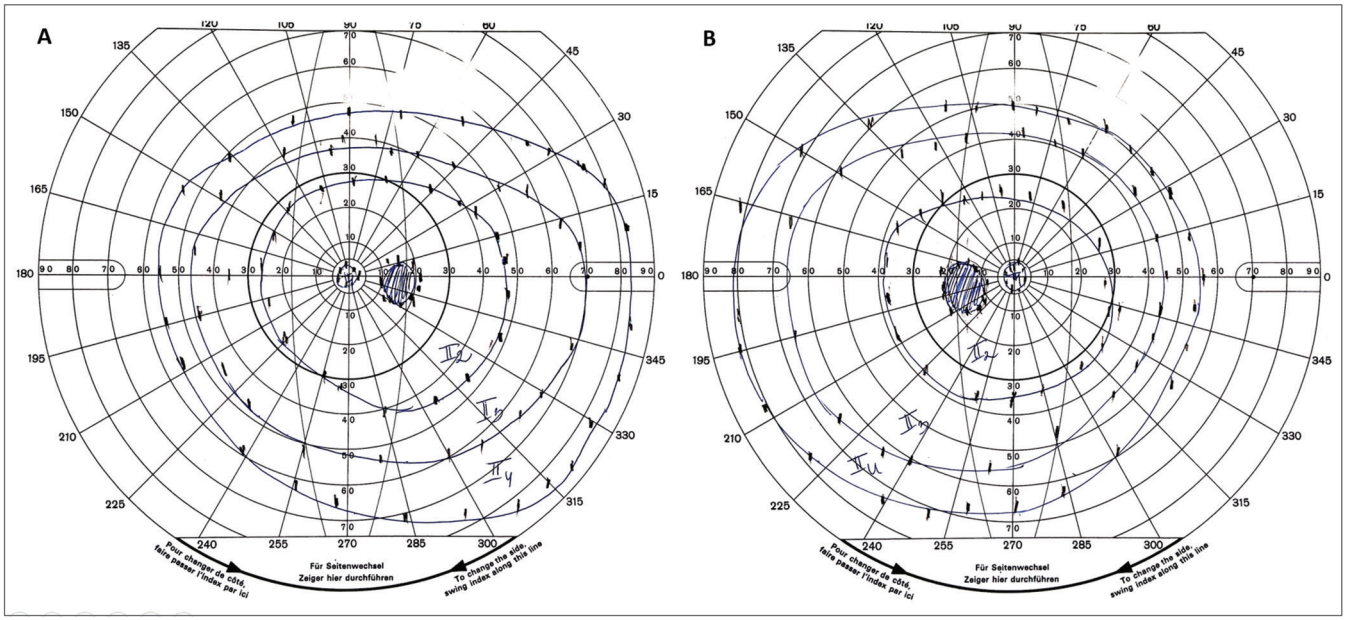

Figure 7: A clinical case; bilateral amblyopia; shows the Goldmann Visual Field at first examination (OU: 0.1).
A) the right eye, B) the left eye. In a typical patient with Leber's hereditary optic neuropathy, we would expect a centrocecal or central scotoma, however in this patient only a narrowed isopter II/1, and a slightly enlarged blind spot are visible bilaterally (the findings can be unreliable due to the very poor visual acuity).

vision in his left eye. He was prescribed corticosteroid therapy for suspected optic neuritis. Two months later, the vision in his right eye started to deteriorate as well. He was referred to the Department of Ophthalmology in Ljubljana for additional diagnostics. At the first examination poor visual acuity (OD: 0.2 Snellen, OS: hand motion) and colour perception impairment (Ishihara OD: 3/15, OS: 0/15) were found. When examining the eye fundi, a hyperaemic optic disk, tortuous vessels and pseudo papilledema were visible in the right eye, while a temporally pale and atrophic optic disk stood out in the left eye (Figure 4A). In the visual field (Goldmann Visual Field examination) a centrocecal scotoma in the right eye and a complete loss of central vision in the left eye were present (Figure 5). Fluorescein angiography was performed, which in both eyes, especially the right, showed markedly tortuous vessels, normal filling time, and an absence of contrast leakage at the optic disk in the late stages (Figure 6). Subsequently, additional diagnostics were performed to rule out infection and demyelination as possible causes of optic neuropathy. The head MRI was unremarkable. Suspecting LHON, genetic testing was performed, which did not identify any of the three typical LHON mutations, but confirmed a new pathogenic variant, G13042T, which was later on found in the patient's cousin with similar symptoms (34). Abstinence from alcohol and tobacco products was advised. No specific treatment was known at that time. The patient's vision subsequently deteriorated to the hand motion in front of the face. He is being monitored regularly. At the last examination in 2020, the state of vision remained unchanged (Figure 4B-D).

6.2 Bilateral amblyopia

Amblyopia is a unilateral, rarely bilateral disorder of visual acuity due to improper stimulation of the visual neurons of the brain in the first years of life, which cannot be improved despite optimal correction of the refractive error, or attributed to a structural defect of the eye or visual pathway. If left untreated, it causes irreversible vision loss in the affected eye (35). Amblyopia is the most common cause of unilateral visual impairment in children. It most often occurs due to strabismus; however, it can also develop in cases of severe anisometropia, ptosis, or congenital cataract (36). It is treated by covering the healthy eye for a few hours a day and by simultaneous sight exercises (37).

Clinical case: A six-year-old boy was treated for deterioration of visual acuity (OD: 0.1, OS: 0.7) in the right eye. Amblyopia was diagnosed and he was prescribed corrective glasses and occlusion therapy for the better left eye. After a year of wearing spectacles and patching, the visual acuity slightly improved (OD: 0.3, OS: 1.0). The boy was monitored regularly; however, there was no significant change in the vision acuity in his right

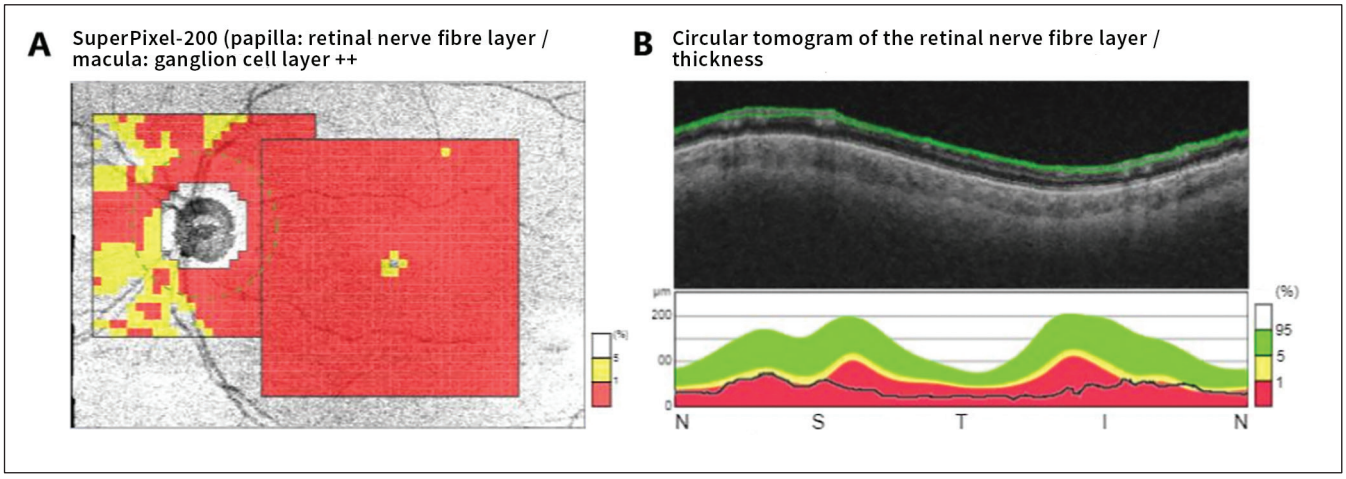

Figure 8: A clinical case; bilateral amblyopia; shows the thickness of the nerve fibres of the macula and optic disk five years after the onset of symptoms.
A) marked thinning of the ganglion cell layer over the entire surface of the macula and temporal thinning of the peripapillary retinal nerve fibre layer, B) optical coherence tomography (OCT) of the optic disk - cross-section.
Legend: N – nasal; S – superior; T – temporal; I – inferior.

eye. At the age of 17, in December 2015, he was seen for an additional deterioration of vision that had occurred four months before. Very poor visual acuity was found bilaterally (OU: 0.1). The examination of the eye fundi revealed pale optic disks bilaterally. In the visual field (Goldmann Visual Field examination) a bilateral narrowing of the isopter II/1 and a slightly enlarged blind spot were present (Figure 7). An OCT of the optic disks showed bilateral thinning of the temporal peripapillary retinal nerve fibre layer. Electrophysiological testing confirmed the presence of neuropathy. Infectious and demyelination causes were excluded. After genetic testing, a diagnosis of LHON with the pathogenic variant G3700A in the mitochondrial genome was made and idebenone therapy was initiated. At the follow-up examination a year and a half later, an additional deterioration of visual acuity was noticeable (OD: counting fingers at 1 m, OS: counting fingers at 1.5 m). The examination of the eye fundi showed even more pronounced pallor of the optic disks. The OCT showed additional thinning of the peripapillary retinal nerve fibre layer, bilaterally centrally and temporally. Brimonidine eye drops were added to the treatment regime due to its possible neuroprotective effect. One year later, visual acuity (OU: counting fingers at 1 m) and the thickness of the retinal nerve fibre layer remained stable. The state of vision at the last follow-up examination in 2020 was unchanged (Figure 8).

Discussion: Although the pathogenic variant G3700A does not belong to the three typical LHON mutations, it is a known cause of LHON. Childhood-onset LHON represents a rare but important phenotypic subgroup that differs slightly in clinical presentation and outcome compared with adult-onset LHON. In the English paediatric cohort study, which included 27 children, it was found that in a good half of the cases (63%) the disease manifests itself as a classic form with an acute onset, in 15% as slowly progressive, and in 22% as insidious or subclinical. Due to the slow progression of the disease, the confirmation of LHON diagnosis can, in some cases take from three to 15 years. The distribution of the three typical mutations is comparable to the one in adulthood (16). The ratio between the male and female sex is estimated at 1.8:1, which could indicate a neuroprotective effect of female sex hormones (38). It is estimated that in about a third of all cases there is a spontaneous partial improvement of symptoms, and even in as many as 60% in those with an acute course of the disease (16,39). Compared to the adult-onset LHON, in which the T14484C mutation shows the highest rate of spontaneous improvement of vision at 40–70%, in the paediatric population, according to the English study, both the G3460A and the T14484C mutation show a high rate of spontaneous improvement at 57% and 43% respectively. In the G11778A mutation, spontaneous improvement is expected in only 23%. As many as 94% of children with the T14484C mutation and 86% with the G3460A mutation had a final visual acuity better than 0.1. Children with the G11778A mutation achieved comparable results in 55% (16,40). A meta-analysis of 67 patients with LHON in childhood suggests a good prognosis, with the final visual acuity better than 0.5 in 39% of children and worse than 0.05 in only 19% of children (16). In very

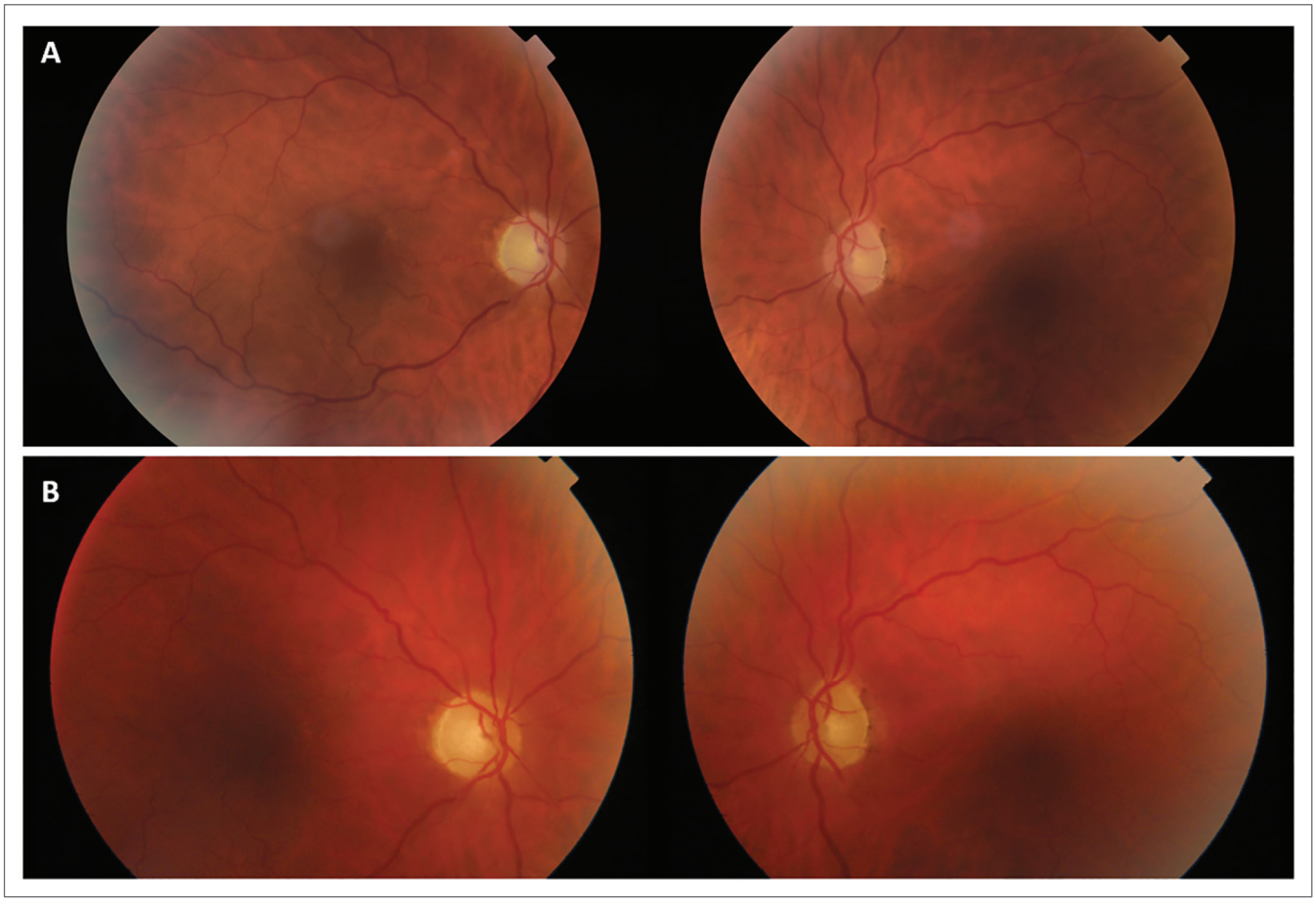

Figure 9: A clinical case; cortical blindness; shows: A) the eye fundi at the first examination, B) five years later. Bilaterally visible pale, atrophic optic disks.

rare cases, the time until the fellow eye is affected can be prolonged for several years. Cases are described in which vision deterioration in the other eye appeared after 12, 16, and even 18 years (41-43).

6.3 Cortical blindness

Occipital lobe strokes are relatively rare. They account for around 5–10% of strokes and are mostly unilateral (44). The main clinical feature is visual impairment, manifested as homonymous hemianopsia or homonymous quadrantanopia. In very rare cases, the stroke can be bilateral, which can lead to central vision loss and total blindness. Confusion, amnesia, ataxia, visual hallucinations, illusions, or anosognosia may be associated with acute perfusion deficits, depending on the extent of the affected area (44,45).

Clinical case: A 57-year-old man was treated in a regional hospital in April 2016 for progressive deterioration of vision in both eyes despite optimal correction with spectacles. Extremely poor visual acuity was found (OD: counting fingers at 2 m, OS: counting fingers at 1 m). On examination of the eye fundi, pale and atrophic optic disks were seen, which is otherwise not characteristic of damage to the visual cortex (Figure 9A). CT and MRI scans of the head were performed, which revealed a 3.1 x 3.6 cm ischemic lesion in the right occipital lobe. A CTA showed 50–60% stenosis of the common and internal carotid arteries. Due to the post-stroke condition, cortical vision loss was suspected. The patient was referred to the Department of Ophthalmology in Ljubljana for additional diagnostics. Half a year later, he was examined for the first time by a neuro-ophthalmologist. In the meantime, visual acuity deteriorated to counting fingers in front of the face with concurrent colour vision impairment and bilateral centrocecal scotoma development. The examination of the eye fundi showed pallor and atrophy of the optic disks. An OCT of the macula and optic disks were performed. The latter showed initial bilateral thinning of the temporal peripapillary retinal nerve fibre layer (Figure 10A). The patient was referred for additional electrophysiological testing. At

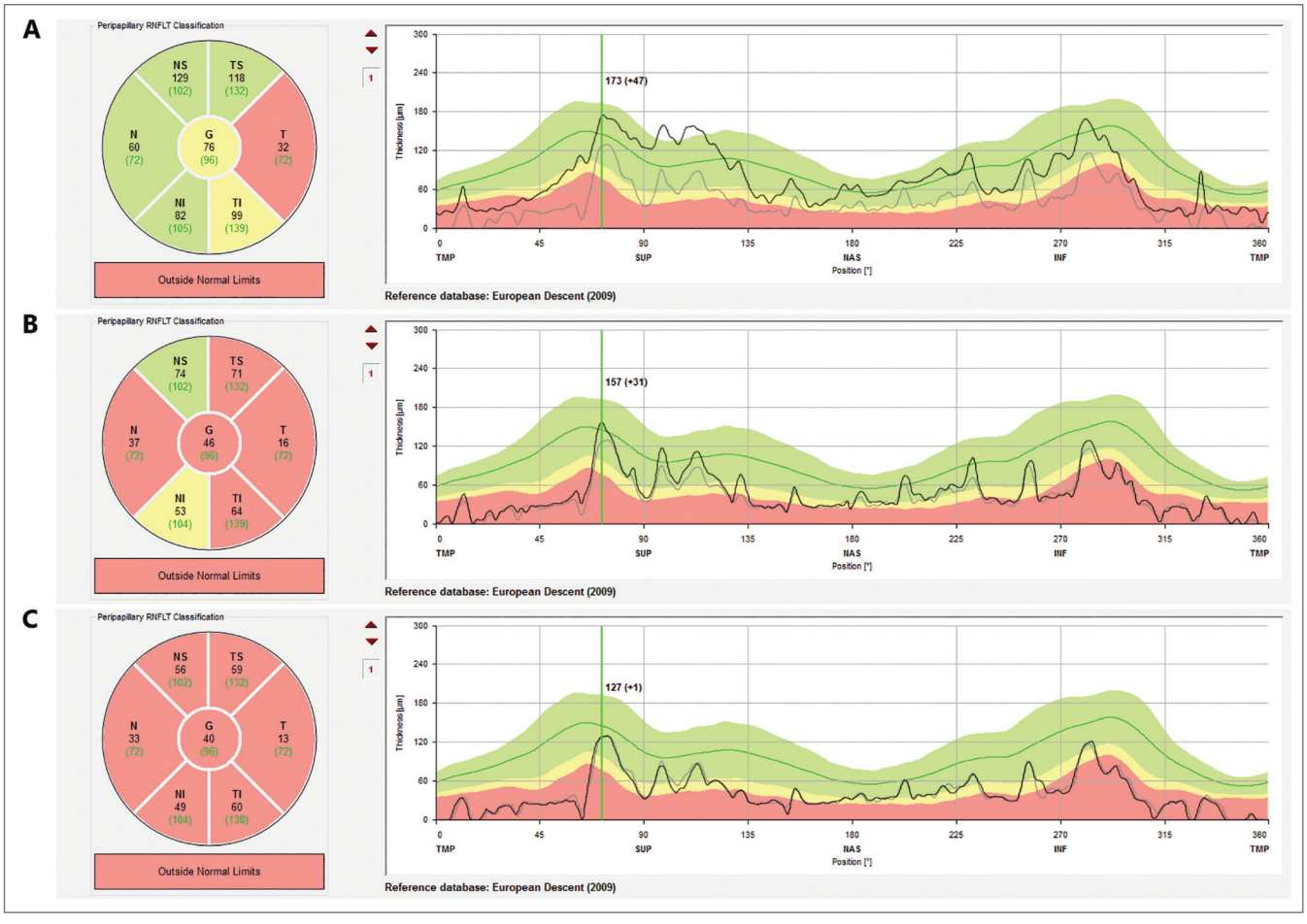

Figure 10: A clinical case; cortical blindness; shows an optical coherence tomography of the optic disk with noticeable progressive thinning of the peripapillary retinal nerve fibres layer over the entire diameter.
A) at the first examination; B) after one year; C) after three years. The green curve represents the mean thickness of the peripapillary retinal nerve fibre layer in a healthy person. The black curve represents the average thickness of the patient's peripapillary retinal nerve fibre layer on the day of the recording, the grey curve represents the comparative result (the average thickness of the patient's retinal nerve fibre layer at the previous or the next recording).
Legend: N/NAS – nasal; SUP – superior; T/TMP – temporal; INF – inferior; NS – nasal superior; TS – temporal superior; NI – nasal inferior; TI – temporal inferior; G – average thickness; peripapillary RNFLT classification – classification of peripapillary retinal nerve fibre layer thickness.

the follow-up examination a year later, the patient gave a more detailed family history of blindness in seven relatives on the mother's side. Electrophysiological examinations showed signs of bilateral impairment of ganglion cell function – a decrease in the PERG N95 wave and signs of severe conduction impairment along the optic nerve – not detectable VEP (20). This kind of pattern showed that this was not only a case of cortical involvement but also of bilateral optic neuropathy with ganglion cell damage. The patient underwent a follow-up OCT, which showed additional thinning of the ganglion cell layer of the retina and the temporal and nasal peripapillary retinal nerve fibre layer (Figure 10B). He was referred for genetic testing for LHON, where a typical mutation in the mitochondrial genome (G11778A) was identified. Treatment with idebenone was initiated. A year later, a partial improvement of vision was observed (counting fingers at 30 cm), with further thinning of the peripapillary retinal nerve fibre layer throughout the optic disk diameter (Figure 10C). Later on, the disease was confirmed in other members of the extended family. The state of vision at the last follow-up visit in 2021 remained unchanged (Figure 9B).

Discussion: LHON should be suspected in all patients with bilateral loss of visual acuity, regardless of age and brain pathology (it may also be due to mitochondrial dysfunction of brain neurons). The confirmation of the diagnosis in this patient led to the identification of a large

family with pronounced symptoms. Many members had already been treated by ophthalmologists; however, the cause of poor vision had not been recognized until then. Since a rapid initiation of treatment with idebenone can improve the course of the disease, the identification and clinical management of all relatives who are possible carriers of the mutation are crucial, as well as genetic testing of symptomatic patients, advising on avoiding smoking and alcohol consumption, and instructions that in the event of vision loss seeing an ophthalmologist as soon as possible is essential.

6.4 Tobacco-alcohol optic neuropathy

Tobacco-alcohol optic neuropathy is a very rare form of optic neuropathy that can occur in people with a history of excessive alcohol and tobacco use. It used to be a common diagnosis in the 20th century, however, with the development of diagnostic methods, it receded into the background and is rarely encountered today, as it is mostly a diagnosis of exclusion. Research shows the disease is primarily composed of two separate processes (46). Due to excessive alcohol consumption and concomitant poor nutrition, a deficiency of vitamin B complex (most frequently B1 and B12) and folate often develops, leading to nutritional optic neuropathy, which shows improvement after vitamin B replacement therapy and a balanced diet (47). In rare cases, especially in older pipe and cigar users, and those chewing tobacco, tobacco optic neuropathy may develop, which recovers within 3–12 months after quitting tobacco products (48,49). The exact pathophysiological mechanism is still unknown. The folate and vitamin B12 deficiencies are thought to affect demyelination of the optic nerve, and free radicals and cyanide in tobacco are thought to affect mitochondrial oxidative phosphorylation (50,51). Both clinical pictures may therefore present similar to LHON with bilateral vision acuity decline, centrocecal scotoma, and accompanying colour vision impairment (52).

Clinical case: A 60-year-old man was treated in a regional hospital in 2001 due to sudden loss of vision in one eye. During the hospitalization, the vision in the other eye also began to deteriorate. A CT scan of his head was performed, which only showed mild frontal lobe atrophy. Infectious and demyelination causes were excluded. After two months, he was admitted to the Department of Ophthalmology in Ljubljana for further diagnostics. Very poor visual acuity was found (OS: hand motions in front of the face, OD: 0.1). On examination of the eye fundi, pink and nasally poorly demarcated optic disks were seen. Goldmann Visual Field test showed extensive bilateral central scotoma. Pattern electroretinogram (PERG) showed the appropriate amplitude of both P50 and N95 waves. Visual evoked potential (VEP) showed bilaterally inadequately formed waves, right a W-shaped wave, and left a prolonged P100 wave latency. Due to the history of long-lasting smoking (20 cigarettes per day) and alcohol consumption, a diagnosis of toxic optic neuropathy was made. The patient was advised to abstain from alcohol and cigarettes and take nutritional supplements and injections of vitamin B12 intramuscularly. His cousin was diagnosed with LHON by chance 17 years later. In 2020, the patient underwent genetic testing that confirmed the typical G11778A mutation. The state of vision remains unchanged.

Discussion: Although LHON most often manifests itself in the second and third decades of life, the possibility of a genetic disorder was not included in the differential diagnosis at the time of examination in 2001 due to the history of long-term smoking and alcohol consumption. Electrophysiological tests already indicated an early conduction impairment along the optic nerve, which would also be characteristic of toxic optic neuropathy. Despite the exclusion of other causes of optic neuropathy, due to risk factors and the absence of positive family history at the time, the opinion in the direction of acquired/toxic neuropathy prevailed. Later research has shown that in the subacute and dynamic phase of the disease, in about 50–70% of patients the PERG N95 wave has a reduced amplitude with concomitant changes in the amplitude and latency of the VEP P100 wave in most cases. The PERG P50 wave mostly remains appropriately shaped with a normal amplitude but slightly shorter latency. This suggests a gradual degeneration of retinal ganglion cells and selective involvement of myelinated nerve fibres. In the chronic phase of the disease, the amplitudes of the PERG N95 wave are reduced in most cases together with markedly reduced and prolonged VEP P100 latencies (34,53). At the onset of spontaneous vision improvement, an improvement in all or only individual electrophysiological parameters can be observed. Cases are described where the improvement occurred despite the absence of electrophysiological changes (34,54,55). With the advancement in the OCT after 2003, the recognition and assessment of the disease have greatly improved, as the OCT allows us to accurately observe the thickness and structure of the nerve fibres of the retina and the optic disk.

7 Conclusion

Leber's hereditary optic neuropathy is a genetic vision

disorder that is rarely encountered in everyday clinical practice. In Slovenia, the prevalence is estimated at 1/72,000, which is lower than reported by the other European studies, and with a higher proportion of atypical variants. It is a rough estimate, based on the data of already confirmed cases and expected confirmations in patients still in the diagnostic process. In the future, it is expected the prevalence of LHON in the Slovenian population will increase as the disease will become more recognized. The diagnosis should be based on good medical history, assessment of functionality and impairment of the optic structures, and confirmation by genetic testing. The patient must be offered genetic counselling, information about potential risk factors and, in the case of a subacute or dynamic clinical picture, pharmacological treatment with idebenone. The path to confirming the disease is often long and requires extensive subspecialty diagnostics. In rare cases, the disease is masked by accompanying neurological symptoms and quite often, especially in children and elderly patients, remains unrecognized or can be mistaken for amblyopia or toxic optic neuropathy, as shown in our cases. LHON must always be ruled out in bilateral, simultaneous or consecutive, painless vision loss, regardless of age and gender. In most cases, adult patients remain permanently impaired or retain a partial degree of visual loss. In children, the disease can manifest with a chronic, subclinical course and shows a greater proportion of spontaneous improvement. In the future, additional studies are needed to improve the understanding of pathophysiological processes, patient management, and treatment.

Conflict of interest

None declared.

Inform consent of the patient

The patients gave informed consent for the publication of their case.

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