COINCIDENCE OF IDIOPATHIC INTRACRANIAL HYPERTENSION AND LEBER HEREDITARY OPTIC NEUROPATHY. A CASE REPORT

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SUMMARY

Goal: This paper describes a case of the long-term monitoring of a patient with optic nerve swelling on the ocular background (papilledema), accompanied by symptoms of intracranial hypertension, on whom a genetic examination was performed as part of the differential diagnosis, confirming Leber Hereditary Optic Neuropathy with the m.3460G>A mutation.

Casuistry: During the examination of a 5-year-old patient after an alleged head injury at a bouncy castle, an optic nerve papilla with unclear boundaries was described in the ocular background of both eyes. Neurological examination, including brain Magnetic Resonance Imaging, was indicated to rule out possible intracranial hypertension. Both examinations yielded a finding within the norm. After 8 years of regular follow-up, the patient attended our clinic with acute problems in terms of sudden visual impairment during baseball training. The performed eye examination revealed a deterioration of the vision of the right eye on counting fingers to 50 cm, vision of the left eye to 0.4 naturally, a slowed photoreaction of the right pupil, prominent optic nerve papilla with unclear boundaries on both eyes, dilated and more coiled vessels with a crossing phenomenon; the retinal periphery shows no focal changes. Due to the swelling of the papilla, acute deterioration of the vision and the suspected intracranial hypertension, the patient was immediately referred for neurological examination and subsequent hospitalization. There, the patient underwent computer tomography of the brain, venography of the dural venous sinuses and an initial laboratory examination that showed no pathology. There was increasing headache, nausea and vomiting throughout the period. A lumbar puncture was performed. The cerebrospinal fluid pressure before sampling was 285 mmH_2O and 100 mmH_2O after sampling. The biochemistry of the fluid was normal, with negative microbiology. Evoked visual potentials had bilaterally prolonged latencies, which corresponds to optic nerve compression. An ophthalmological examination ruled out a drusen papilla. Using Optical Coherence Tomography, a 600 µm edema was detected. The patient underwent two relieving lumbar punctures, which led to a subjective improvement, without objective improvement. Finally, the neurosurgeon referred the patient for ventriculoperitoneal drainage. Due to the impaired vision and lack of response to the therapy induced, a genetic test was performed, which confirmed Leber Hereditary Optic Neuropathy with the mutation of m.3460G>A.

Conclusion: Despite the substantially improved identification of the Leber Hereditary Optic Neuropathy, the diagnosis may still be significantly delayed. The variability of initial findings, the rare incidence of the disease and few well-defined symptoms of the disease lead to significant diagnostic difficulties and late commencement of treatment. It is not possible to say whether there was a coincidence of IIH and LHON, or whether the signs of IIH are a possible concomitant of the acute phase of LHON.

Keywords: Leber Hereditary Optic Neuropathy, idiopathic intracranial hypertension, pseudotumor cerebri, congestive papilla, papilledema, optic nerve papilla swelling

INTRODUCTION

Idiopathic intracranial hypertension (IIH), or pseudotumor cerebri, is a rare neurological disease of unknown etiology, characterized by high cerebrospinal fluid pressure ≥ 280 mmH_2O [1] with no apparent cause [2], probably related to disturbed dynamics of the cerebrospinal fluid [3]. Visual impairment is a major concern in this disease [1], as it causes optic nerve atrophy [3]. IIH manifests within pediatric patients usually in one of two ways: either through symptoms of increased intracranial pressure and papilledema, or through an incidental finding of papilledema during a routine examination of an otherwise asymptomatic child [4]. The swelling of the papilla is generally bilateral, but can be asymmetrical or unilateral [5]. It

is important to distinguish papilledema from pseudopapilledema to avoid potentially harmful over-diagnosis, over-investigation and over-treatment. The use of imaging methods is appropriate for monitoring the dynamics of findings in the ocular background. It may, however, be impossible to acquire images of the ocular background and to carry out imaging with Optical Coherence Tomography (OCT) in the pediatric population, due to age and lack of cooperation. In such situations, using the Frisen scale [4] to document the severity of the edema of optic nerve papilla may be appropriate. Many diagnoses can mimic papilledema, such as the atypical appearance of the optic nerve target (oblique optic nerve insertion, tilted disc), optic disc drusen or optic neuropathy with swollen optic nerve target, attributable to pathology different from intracranial hypertension [6].

Leber Hereditary Optic Neuropathy (LHON) is a blinding disease with a maternal mode of inheritance. This condition was described in 1871 by Theodor Leber [7]. Over 95 % of patients carry one of three prevalent point mutations in mitochondrial DNA genes: m. 11778G>A, m.3460G>A and m.14484T>C [8]. Development of symptoms of this disease does not occur in every individual with the identified LHON-associated mutation [9]. The clinical symptoms usually develop between 15 and 35 years of age, and the disease manifests in 90 % of patients by the age of 50 years. The effect on one and the other eye occurs either simultaneously or several weeks apart [8]. Approximately 60 % of patients with LHON are aware that they have LHON in their family history, but 40 % of them deny having a known family history [10]. Vision loss is usually the only symptom of the disease, although families with other symptoms have been recorded. This condition is described as "LHON plus" and, together with vision loss and optic nerve atrophy, includes movement disorders, tremor and heart rhythm disorder [11].

CASUISTRY

A boy born in 2007 has been monitored in our Outpatient Clinic since May 2012, when he arrived for a post-injury examination. Two days before the examination, he allegedly hit his head on a bouncy castle pole. He did not lose consciousness, did not feel nauseous and subjectively felt well. According to his personal history, his mother's pregnancy was physiological, and the delivery was performed by Caesarean section due to the pelvic end position of the baby. Allergological history was negative. The family history was insignificant. According to the family eye history, the mother had myopia. When examining the vision of both eyes, the patient's visual acuity was 1.0 naturally.

Objective findings of the examination showed a hematoma and a small excoriation on the right (probably in the eyelid area, but the medical records do not specify exact localization), a slowed photoreaction on the right, a papilla with unclear borders in the ocular background of both eyes; otherwise without any traumatic changes. Due to the incipient congestive papilla of both eyes and a suspected pseudotumor cerebri, the patient was referred for a neurological examination. The neurologist diagnosed the child's hyperactivity, otherwise the neurological findings were without any topical changes; association of the ocular findings with the trauma within the skull was unlikely. The neurologist recommended Magnetic Resonance Imaging (MRI) of the brain. The MRI showed normal brain findings, hyperplastic mucosa in the right maxillary sinus and ethmoid and sphenoid sinuses. Monitoring was recommended. Periodic check-ups were carried out every three months, with the findings in the ocular background being the same. Due to the diagnosis of congestive papilla of both eyes and a suspected pseudotumor cerebri, an examination at the General University Hospital in Prague was carried out in May 2013. The patient reported headaches in the forehead region, usually in the evening, sometimes alleged diplopia in the evening, but was unable to be more specific about the findings. Examination of the vision in both eyes detected a natural visual acuity of 6/6, intraocular pressure was within normal limits. Other eye examinations and tests yielded good results, hyperemic, unbounded, elevated papilla, without hemorrhages or cotton wool deposits, without dilatation in the venous system or other changes in the fundus were described in the ocular background.

Conclusion: "The findings on the papilla are beyond normal, they appear to be congestive papilla, we expect intracranial overpressure, on the other hand, however, any other congestion- related difficulties are absent. In addition, congestion in children after closing the fontanel is always accompanied by rapid progression of the finding; our patient, however, has had 9 months without further apparent progression. The alleged diplopia or impaired mobility could not be proven."

During the examination in Prague, it was recommended that the diplopia be examined, as well as a follow-up MRI of the brain to be carried out. Invasive examinations such as fluorescence angiography were not indicated at the time. The follow-up MRI was performed in June 2013, with normal brain findings. Eye examinations were then performed every 6 months, with the same findings and the patient did not experience any difficulties. A follow-up examination at the General University Hospital in Prague was performed in July 2015. Vision in both eyes was 1.0, intraocular pressure was normal. Normal findings were found in the anterior segment, the micro exodeviation was safely within the fusion limits, isocoria with normal reactions of pupils, the papillas were prominent in the ocular background, no hemorrhages, the vessels were more coiled but without increased venous filling, merely a fuller capillary network. According to the ultrasound, it was not possible to

rule out a small drusen of the optic nerve target on the right and drusen were not detected on the left. Drusen were not found by autofluorescence on OCT either. A normal field of view was described on the perimeter bilaterally, although with lower reliability, but the blind spots were not enlarged.

Conclusion: "Although the ocular findings are beyond the normal range, the long-term normal function does not support a diagnosis of pseudotumor cerebri."

Regular check-ups were recommended, which took place in our clinic every 6 months. The results of attempts to assess the visual field and OCT were not valid, due to the high error rate and the presence of numerous artifacts. The ocular background remained unchanged throughout the follow-up period (Figure 1).

In August 2020, the patient arrived at our clinic with acute visual impairment suffered during baseball training. He was allegedly hit in the left eye by a baseball a week before the examination, causing blurred vision. Visual acuity of the right eye corresponded to finger counting at 50 cm naturally, the left eye was 0.4 naturally, intraocular pressure of the right eye was 13.8 mmHg and 11.9 mmHg in the left one, autorefractometry of the right eye was -1.25-0.50/129 and -1.25-0.25/66 in the left eye; correction did not improve vision. Objectively, we found no pathology in the anterior segment, the right pupil reacted with delay. In the ocular background, we saw a prominent papilla on both sides, with unclear borderlines and with line-shaped hemorrhages, vessels were dilated and coiled with a crossing phenomenon, the retina to the periphery was without focal changes (Figure 2).

OCT examination of the optic nerve papilla (OCT/SLO RetinaScan Nidek RS-3000) was performed – an image of

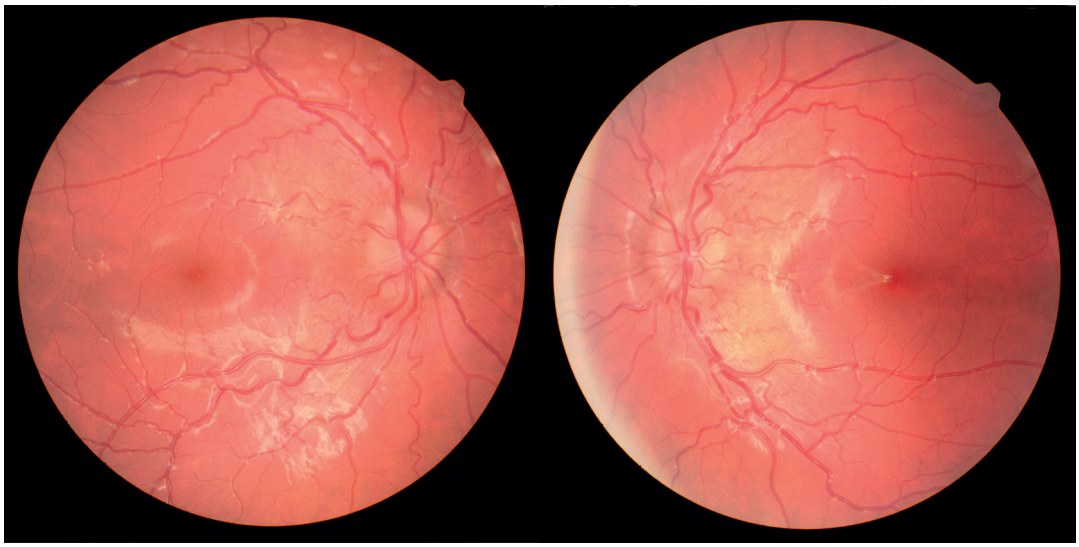

Figure 1. A photo of the patient's ocular background (July 2015)

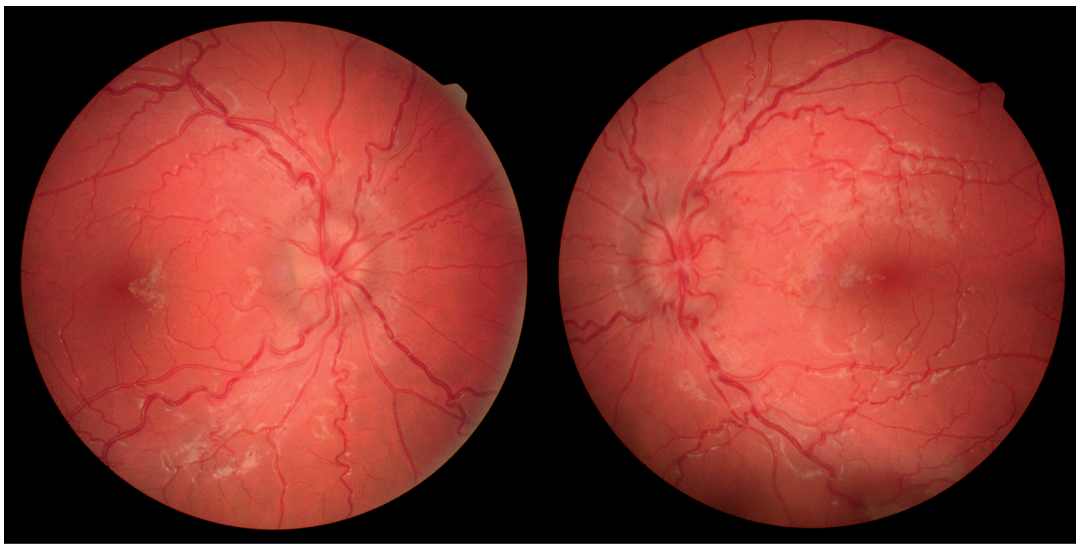

Figure 2. A photo of the patient's ocular background (August 2020)

the nerve fiber layer swelling in both eyes was found (Figure 3). Due to swelling of the papilla, the acute deterioration of vision and the suspected intracranial hypertension, we referred the patient to the Neurological Clinic at Olomouc University Hospital, where he was subsequently hospitalized.

During the hospitalization, computer tomography of the brain was performed but proved no pathological changes (MRI could not be performed due to the presence of fixed braces); neurological examination did not show any signs of central nervous system focal lesions. The venography of the dural venous sinuses did not detect any filling defects, and no detection of thrombosis. The initial laboratory examination did not indicate any obvious deviation from the norm. Headache, nausea, and vomiting progressed during hospitalization. A lumbar puncture (LP) was performed: cerebrospinal fluid pressure before sampling was 285 mmH_2O and 100 mmH_2O after sampling, biochemistry of the fluid was normal, and its microbiology was negative.

Visual evoked potentials were conducted; there were prolonged latencies on both sides, which corresponded to a case of optic nerve compression. Ophthalmological examination: vision of the right eye via a finger test was 30 cm, vision of the left eye was 6/24. The anterior segment was calm, pupils were round, isochoric, direct, and indirect reactions were equipotent, there was no afferent pupillary defect. Fundus in mydriasis: vitreous was clear, papilla was above the niveau, edges were blurred, hemorrhages were not present, spacing of vessels was regular, vascular pattern on papilla was more pronounced, vessels to periphery were more coiled, the venous system in particular, macula with reflex, retina attached to periphery, no focal changes.

Ultrasound examination ruled out a papilla drusen. OCT detected a 600 µm edema. The case was concluded as "Congestive bilateral papilla – according to the parère, pseudotumor cerebri has been suspected since 2012". Headache, nausea, and vomiting progressed during the hospitalization, the patient had his head persistently tilted, which complicated the examination. Due to the slight improvement of the difficulties after the LP and a small improvement in vision (vision of the right eye via finger test was 1 m and 6/18 in the left eye), it was recommended to use acetazolamide 250 mg tablets 3 times a day, as well as a consultation with a neurosurgeon concerning an indication for the introduction of a shunt. After the second alleviating LP, the neurosurgeon finally referred the patient for ventriculoperitoneal drainage.

On discharge, the patient subjectively felt improvement in vision, more in the evening, without pain or vomiting. The right eye vision via finger test was 1 m, the left eye vision was 6/60, correction did not improve the vision; intraocular pressure on the right was 11 mmHg and 12 mmHg on the left, autorefractometry of the right eye was –0.50–0.50/159 and –1.25 of the left eye. OCT examination showed a minimal reduction in edema of

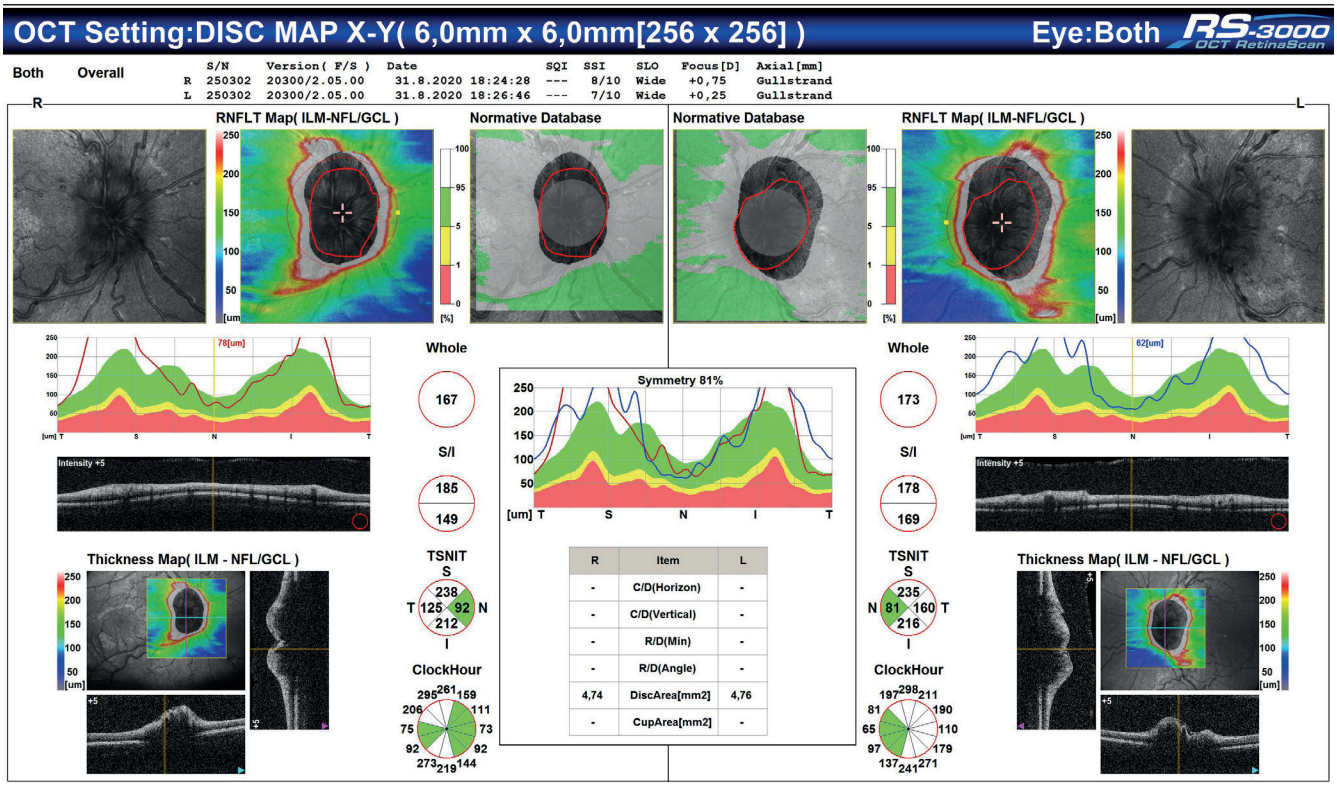

Figure 3. OCT of the patient's papilla – image of swelling of the nerve fiber layer in both eyes (August 2020)

the nerve fiber layer. Objectively, the anterior segment was calm, papilla with edema was present in the ocular background, stable or perhaps slightly less edematous vessels without ingrowth, the hemorrhage around the papilla was absorbed, the dilatation of veins reduced. Subjectively improved vision without an objective improvement. The neurologist concluded the diagnosis as follows: "Pseudotumor cerebri, the patient underwent ventriculoperitoneal shunt under general anesthesia."

After the hospitalization, regular check-ups at the Neurosurgical Clinic and E ye Clinic were recommended. Due to progressive deterioration of the visual pathway conduction according to visual evoked potentials, genetic testing was added to the differential diagnosis, which confirmed Leber Hereditary Optic Neuropathy (LHON), a mutation in m.3460G>A (>96 % heteroplasmy in peripheral blood). The patient was transferred to the General University Hospital in Prague for Idebenone therapy. The same mutation was found in the blood of the patient's mother and in the blood of the patient's sister.

Both parents and the patient's sister are being monitored by our clinic as well. The parents have a minor eye finding. The sister (year of birth 2009) has been monitored in our Outpatient Clinic since 2010, due to tear duct obstruction, without any other ocular pathology. In 2016, there were normal ocular findings, save for a slightly unbounded optic nerve papilla. The patient did not have any subjective difficulties, therefore we recommended regular check-ups by an ophthalmologist. In 2017, we described a prominent papilla with unclear boundaries in the ocular background, with no hemorrhages (Figure 4). According to the performed OCT examination of the patient's sister (OCT/SLO RetinaScan Nidek RS-3000), we concluded the finding as a pseudoedema of the optic nerve papilla (Figure 5). We continue with the monitoring; we found no progression of the findings during the last check-up in 2020.

DISCUSSION

From the very beginning of the patient's monitoring, we could see the papilla in the ocular background with unclear boundaries, above the niveau, the vascular pattern on the papilla more pronounced, the vessels more coiled, without any visual impairments. Repeated neurological examinations to exclude intracranial hypertension and MRI showed no neurological pathology. Historically, LHON has been divided into 3 distinct clinical groups: sub-clinical mutation carriers, patients with acute LHON (with duration of the disease of 1 year or less), and patients with chronic LHON (with duration of the disease of more than 1 year) [12]. Changes in fundus examination and OCT measurements, including vascular abnormalities, may be evident with unaffected carriers of LHON-associated mutations [12]. Three clinical features unique to LHON can be observed: vascular tortuosity, peripapillary swelling of the nerve fiber layer and peripapillary telangiectatic vessels; peripapillary hemorrhage may occur [9]. These changes can also be seen in the patient's sister's ocular background. However, neither gender nor causal mutations affect when the disease manifests and how severe the loss of visual function will be. Males are 4-5 times more likely to develop the disease [8]. It can be said that vascular changes may serve as useful objective measures of the disease. Individual reports concerning vascular changes in LHON 11778 and 14484 have been reported, but an isolated vascular evaluation of the primary mutation variant in LHON 3460 is absent [13]. In addition, no other clinical abnormalities were found in any of the affected from the mother's genes with the m.3460G>A mutation [14].

On examination of the patient after a sudden deterioration of vision during training and trauma to the left eye, we observe a progression of bilateral papilledema,

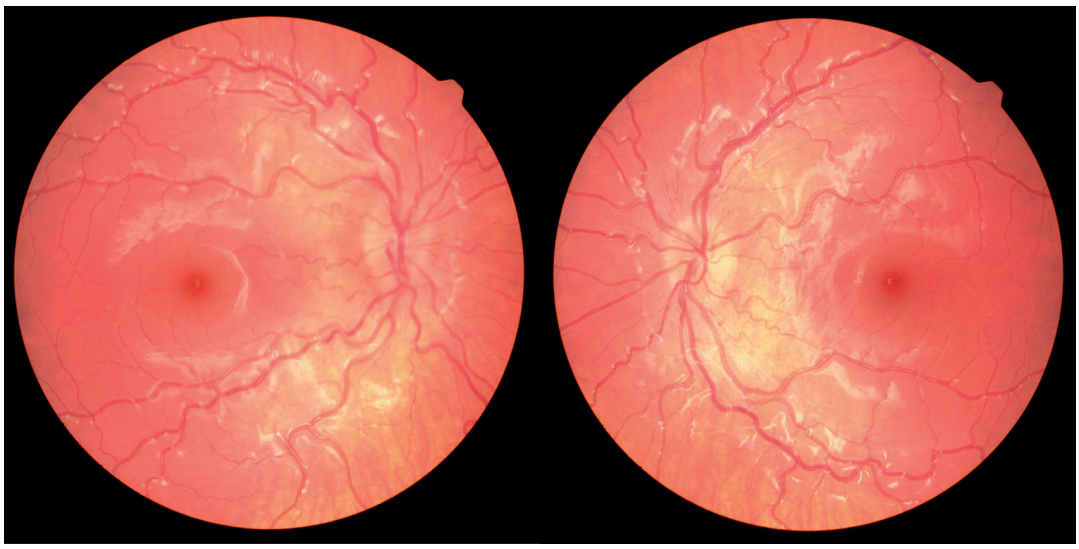

Figure 4. A photo of the patient's sister's ocular background (2017)

obliteration of the optic nerve papillae boundaries – a finding that is considered characteristic of the IIH [5]. This is followed by headaches, deterioration of vision, practically up to blindness, which is the main clinical symptom of the disease [1]. The patient met the criteria for IIH as proposed by Friedman, which include: normal neurological examination, presence of papilledema, normal results of computed tomography and MRI of the brain, normal cerebrospinal fluid composition, and elevated opening pressure during lumbar puncture (≥ 250 mmH_2O in adults and ≥ 280 mmH_2O in children (250 mmH_2O when the child is not obese and not sedated)) [1]. Accurate diagno-

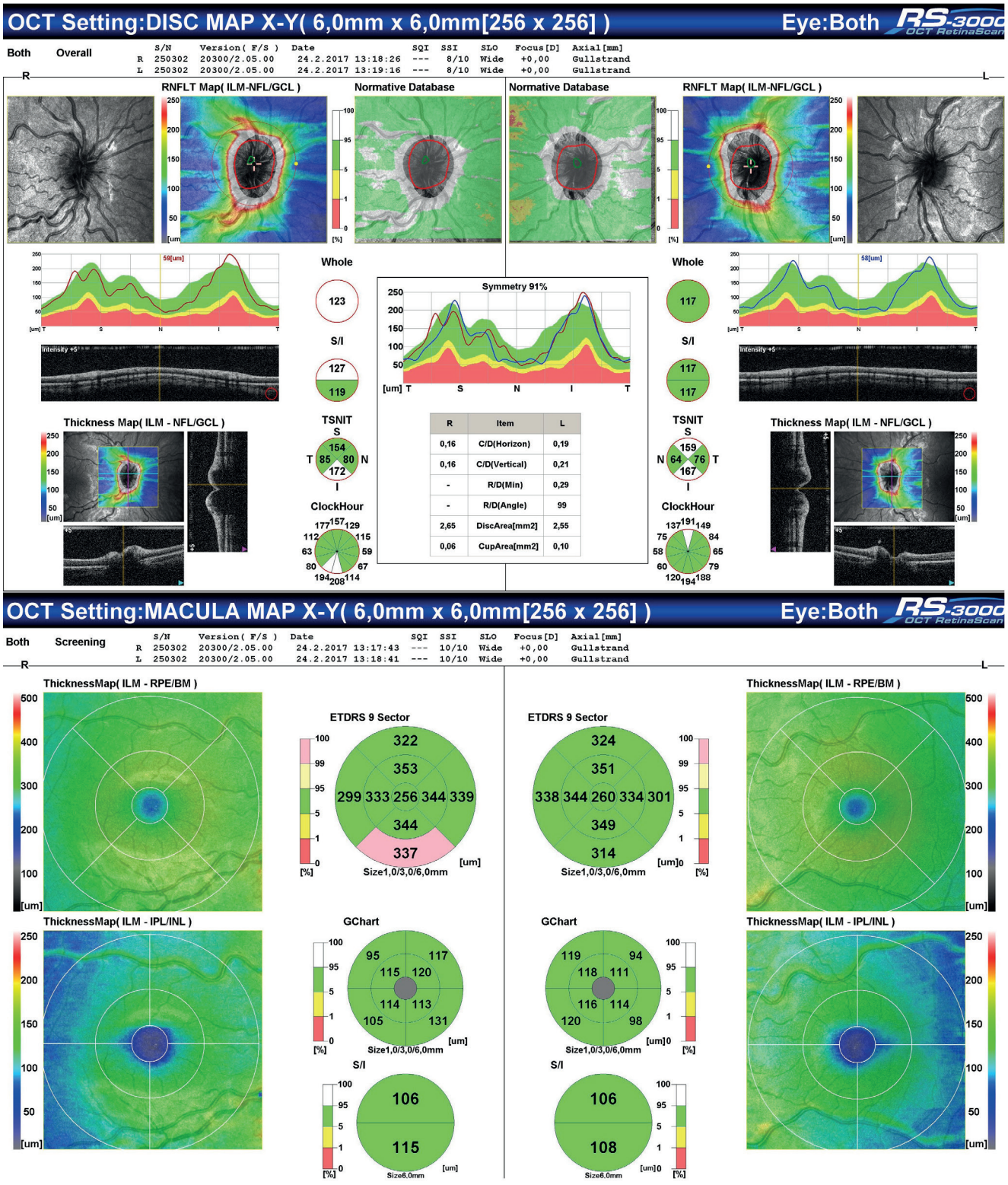

Figure 5. OCT of the patient's sister – pseudoedema of the optic nerve papilla (2017)

sis required measurement of opening pressures and the analysis of cerebrospinal fluid [6]. Unlike IIH, LHON usually manifests as acute to subacute, bilateral, sequential, and painless loss of vision [15] due to impaired function and loss of retinal ganglion cells, ultimately leading to optic nerve atrophy [7]. According to the records from OCT examinations, the swelling of the papilla was increasing; after performance of the LP, the patient subjectively felt improvement with respect to the discomfort and vision, which is also indicative rather of intracranial hypertension, although some cases of hereditary optic neuropathies with clinical signs of idiopathic intracranial hypertension might respond to treatment for reduction of intracranial pressure [11]. A number of medical and surgical interventions may help to reduce intracranial pressure [1]. The treatment includes the use of acetazolamide, topiramate and corticosteroids [4]. However, nearly 10 % of children will eventually require surgery due to the permanent headache or loss of vision [16]. This may include the placement of a ventriculoperitoneal or lumboperitoneal shunt [4]. Although various medical and surgical strategies have been used in IIH cases in pediatric patients, there are no established treatment procedures [17]. Our patient underwent ventriculoperitoneal drainage with favorable structural findings, subjective improvement of vision, but no improvement of objective findings and visual functions.

The literature describes a similar case of an 8-year-old boy with progressive bilateral loss of vision and intermittent headaches, in whom the ocular background examination showed mild optic disc elevation on both sides; the lumbar puncture identified an intracranial hypertension with an opening pressure of 320 mmH2O, normal cell count and protein and glucose levels. Acetazolamide therapy was commenced, which improved the headaches, but the impaired visual acuity remained. Furthermore, targeted mutation analysis for LHON was conducted, which confirmed homoplasmy for the m.11778G>A mutation [18]. Both cases may serve as an example of the course of LHON in children, which is different from the usual course of onset of LHON in adult patients. LHON is often suspected by an ophthalmologist or neurologist [8].

Unfortunately, it is not possible to refer every patient with a suspicious finding in the ocular background for genetic testing. Despite the substantially improved recognition of LHON, there may still be a significant delay in diagnosis [12]. The gold standard of laboratory diagnostics is molecular genetic analysis of prevalent mutations in blood samples or cells of buccal mucosa. This examination is carried out in patients with already developed visual impairment as a part of the differential diagnosis of LHON, or in family members who do not yet have clinical difficulties [8]. In September 2015, the first and, to date, the only drug for the treatment of Leber Hereditary Optic Neuropathy was approved in the European Union. The drug is idebenone (Raxone®), which is effective in respondents, even when started 1 year after the first onset of symptoms [19]. Currently, the therapy is not recommended for relatives of patients with LHON, but lifestyle counselling is recommended [12].

CONCLUSION

The described case demonstrates that, although medicine today is very progressive, there are still diseases whose exact course is as yet unknown. The variability of initial findings, rare incidence of the disease and too few well-defined symptoms lead to significant diagnostic difficulties and late commencement of treatment. It cannot be said whether there was a coincidence of IIH and LHON or whether the signs of IIH are a possible concomitant of the acute phase of LHON. For this reason, this work may be a valuable illustration of the symptoms and course of LHON with the m.3460G>A mutation.

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