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Wolfram Syndrome: A case report of two sisters Wolfram Syndrome: Case report of two sisters

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A R T I C L E I N F O

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A B S T R A C T

Purpose: To present a case of two siblings with optic atrophy associated with Wolfram Syndrome.
Observations: Two young adult siblings presented with serious bilateral loss of vision and dyschromatopsia established in early adolescence. They were referred with a presumed diagnosis of Leber's Hereditary Optic Neuropathy. At baseline, visual acuity was 20/400 in the right eye and 20/200 in the left eye in patient A and 20/200 in both eyes in patient B, color perception tested with pseudo-isochromatic plates was 0/17 in each eye, optic discs were pale, visual field testing revealed diffuse scotomas bilaterally while electrophysiology showed delayed prominent positive deflection (P100) values in both patients. Personal history revealed Type 1 diabetes mellitus since early childhood. Patients were lost to follow-up and presented 4 years later with significant VA decrease (<20/400) and suspected hearing loss. At that point, genetic testing revealed a pathogenic variation in the WFS1 gene thus confirming the diagnosis of Wolfram syndrome. Treatment with idebenone was proposed, to which only one of the siblings agreed. The other patient remained under observation, as no known treatment for optic atrophy in Wolfram syndrome exists to date.
Conclusions and importance: Wolfram syndrome is a rare neurodegenerative genetic disease associated with diabetes mellitus, optic atrophy and deafness. Careful and detailed medical and family history led to appropriate testing that confirmed the diagnosis of Wolfram syndrome. To this day, there is no definite treatment for this disease, but the experimental use of idebenone has been suggested to improve visual function. Genetic testing of family members and offspring of patients is strongly recommended.

1. Introduction

Wolfram syndrome, also known as Diabetes Insipidus, Diabetes Melitus, Optic Atrophy and Deafness (DIDMOAD), is an autosomal recessive neurodegenerative disease of very rare occurrence.[1] Early onset Diabetes Mellitus and optic atrophy are usually the first manifestations of the syndrome and presenting typically in childhood.[1] Wolfram syndrome is caused by a pathogenic variation in the WFS1 gene (4p16.1 chromosome), which encodes wolframin, a transmembrane protein found in the endoplasmic reticulum.[2,3] There is no definite treatment for the disease, although research focuses on regenerative and gene therapy.[4,5]

We report a case of two siblings with Wolfram syndrome documented **by** genetic analysis of the WFS1 gene.

2. Case report

Two siblings, aged 21 and 23 years old, were referred with gradual bilateral vision loss as their primary complaint and a presumed diagnosis of Leber's Hereditary Optic Neuropathy (LHON). Past medical history revealed that both siblings suffered from Type 1 Diabetes Mellitus, manifested at 6 and 2 years of age, respectively. Past ophthalmologic history was negative, apart from gradual loss of vision over several years, of undefined onset.

On presentation, best-corrected visual acuity (BCVA) was 20/400 (logMAR: 1.30) in the right eye and 20/200 (logMAR: 1.00) in the left eye for patient A (21 years old) and 20/200 (logMAR: 1.00) in the right and in the left eye for patient B (23 years old). Color perception was 0/17 in each eye in both patients, tested with Ishihara pseudoisochromatic

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Fig. 1. Fundus Fluorescein angiography (late venous phase), left eye.

Fig. 2. Infrared fundus photo, left eye.

plates. IOP was 17/18 mmHg for patient A and 18/18 mmHg for patient B. Relative Afferent Pupillary Defect was negative for both patients. Fundus examination and fluorescein angiography revealed pale optic discs with no signs of diabetic retinopathy, in both patients (Figs. 1–3). Slit lamp examination was otherwise unremarkable. Optical Coherence Tomography (OCT) revealed retinal nerve fiber layer (RNFL) thinning in the peripapillary area, most prominent temporally, and mildly reduced retinal thickness, especially in the periphery in both patients, in a similar way (Figs. 3, 4, 7 and 8). These OCT findings are common in Leber Optic Neuropathy and Wolfram syndrome.11, 12 Visual field testing showed diffuse deep scotomas (Fig. 5). The patients consequently underwent electrophysiology testing. Electroretinogram (ERG) as tested with the ISCEV protocol showed decreased electric retinal activity bilaterally for patient A (Max Response was 161.4 μV/40.5 ms in the right eye and 180.9 μV/40 ms in the left eye), and in the right eye of patient B (Max Response was 168.9 μV/41.5 ms) and was normal for the left eye of patient B (Max Response was 290.1 μV/42 ms, Fig. 6). Both patients exhibited impaired conductivity of the optic tract with the Visual Evoked Potentials revealing delayed P100 wave with reduced amplitude (Patient A, right eye P100:3.6μV/110.3 ms, left eye: P100: 3.0μV/112.2 ms – Patient B, right eye: P100: 5.4 μV/127.9 ms, left eye: P100: 4.9 μV/128.9 ms).

At that point, the diagnosis of optic atrophy of undefined cause was confirmed. However, both patients failed to return for follow-up and further diagnostic testing.

Four years later, both patients reappeared with significant BCVA deterioration (hand movements for patient A and 20/400-logMAR: 1.30 for patient B). Slit lamp and fundus examination revealed no new findings. Patients additionally underwent autofluorescence imaging and fluorescent angiography, which revealed extensive optic atrophy without signs of diabetic retinopathy or inflammatory retinal disease. No significant variations were noted between the two patients, concerning the optic atrophy. Additionally, both patients showed signs of neurosensory hearing loss. Based on their history (Diabetes Melitus and hearing loss), the patients were referred for genetic testing on their second visit. Since they exhibited three major components of the syndrome, namely optic atrophy, diabetes mellitus and hearing loss, patient samples were analyzed not only for Leber's Hereditary Optic Neuropathy but also for Wolfram Syndrome.

For the genetic analysis total genomic DNA was extracted from whole blood samples on an iPrep purification instrument using the iPrep PureLink gDNA Blood Kit (Invitrogen, Life Technologies, Carlsbad, CA) according to the manufacturer's instructions. This study adhered to the tenets of the Declaration of Helsinki and the ARVO statement of human subjects. Written consent was obtained from subjects participating in this study and the research was approved by the human research ethics committee at the University Hospital of Heraklion, Crete. DNA was analyzed by direct sequencing of all 8 exons and intron-exon junctions of the WFS1 gene following PCR amplification with PCR primers designed using the Web Primer program for PCR and Sanger sequencing conditions.[6]

Nucleotide sequences were compared with the published DNA sequence of WFS1 gene (GenBank accession number NG_011700.1) and cDNA (GenBank accession number NM_006005.3). For the WFS1 gene, cDNA numbering +1 corresponds to A in the ATG translation initiation codon of WFS1 transcript.

Genetic Analysis revealed that the patients were homozygous for the NM_006005.3(WFS1):c.1243_1245delGTC (p.Val415del) pathogenic variation, responsible for the Wolfram Syndrome, thus confirming the diagnosis. C.1243_1245delGTC in the exon 8 of the WFS1 gene, is a deletion of 3 GTC nucleotides in both alleles, in nucleotides c.1243_1245 of the coding area of the gene. On a protein level, this deletion causes an in-frame deletion of valine 415 of the WFS1 protein, resulting in a mutated protein shorter by 1 amino acid (889 instead of 890). The

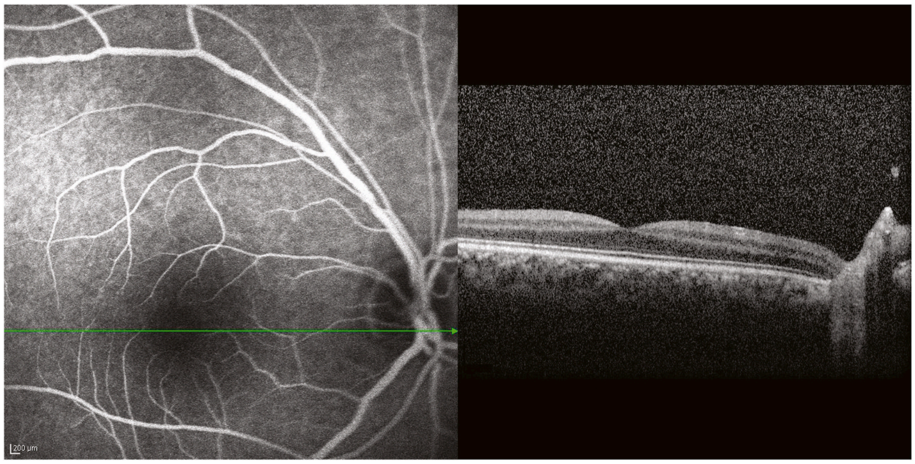

Fig. 3. Fundus fluorescein angiography, late venous phase and macular OCT scan, left eye.

genetic result was identical for both patients.

The p. Val415del variant in WFS1 has been reported in 10 individuals with Wolfram syndrome[7-15] and segregated in 7 affected relatives.[7,9,10,14,15] All these individuals were homozygous or compound heterozygous. This variant has also been reported in ClinVar (Variation ID: 215,406). This variant was identified in 9/33,582 Latino chromosomes by the Genome Aggregation Data base (gnomAD, http://gnomad.broadinstitute.org; dbSNP rs750767821); however, its frequency is low enough to be consistent with a recessive carrier frequency. In addition, in vitro studies suggest that the p. Val415del variant may impact expression of WFS1 (Rendtorff 2011).[13] In summary, this variant meets the criteria to be classified as pathogenic for autosomal recessive Wolfram syndrome based upon reported familial cases, low frequency in controls, and functional evidence including the established association between the WFS1 gene and the patients' phenotype.

Since no designated treatment for optic atrophy in the context of Wolfram syndrome is currently available, patients were advised to begin treatment with idebenone. Patient A agreed and an initial six-month protocol of Raxone®, was prescribed, while the other patient remained under observation. The second patient did not want to commence any treatment.

3. Discussion

Wolfram syndrome is a rare autosomal recessive genetic neurodegenerative disease characterized by juvenile onset Diabetes Mellitus, Optic Atrophy, Diabetes Insipidus and Deafness.[1] The prevalence of Wolfram syndrome is estimated between 1 in 100,000 and 1 in 770, 000.[1,16]

Patients usually present with diabetes mellitus around the age of 6, while optic atrophy manifests at an average age of 11 years.[1] Diabetes insipidus and sensorineural hearing loss are present in 70% and 65% of the cases, respectively.[1,17] Other manifestations include urinary tract anomalies, ataxia, neuropsychiatric disorders and olfactory defects, which vary in prevalence among patients.[1,18] Median age of death is 30 years, usually as a result of respiratory failure secondary to brain stem atrophy.[1] Mortality rate in Wolfram syndrome is much higher than in type I diabetes, with 60% of the patients with Wolfram syndrome dying by the age of 35.[19]

Optic nerve atrophy as a result of retinal ganglion axon death is the most common ophthalmic finding in Wolfram syndrome and can lead to the diagnosis of WFS in 39% of the cases.[18] Optic atrophy manifests as constriction of visual fields, color perception deficiencies, especially in the blue-yellow spectrum and loss of visual acuity which, contrary to Leber's hereditary optic neuropathy, may be of variable rate and is usually gradual (1–25 years).[20]

Thinning of the RNFL and the macula is the main OCT finding.[11,21] OCT-angiography shows reduction in the peripapillary microvasculature, most prominent in the temporal area.[22]

Electrophysiology tests in Wolfram syndrome are indicative of the optic atrophy. Specifically, electroretinography may vary but is usually normal, while visual evoked potentials show a delayed P100 value with reduced amplitude and abnormal wave morphology.[23–25]

Notably, diabetic retinopathy is rare among patients with Wolfram syndrome, in spite of the early development of diabetes mellitus and poor glycaemic control in general. One possible explanation is that retinal vessel attenuation due to optic atrophy could protect the retina from glucose toxicity.[10,23–25]

3.1. *Genetics-wolframin*

The recessive mode of inheritance, in addition to the similarity of Wolfram syndrome to Leber's Hereditary Optic Neuropathy (LHON) and Myopathy, Encephalopathy, Lactic Acidocis and Stroke-Like episodes (MELAS) has originally led the search of the genetic basis of the syndrome to mitochondrial DNA mutations.[26,27] However, in 1998, the responsible gene (WFS1) was identified on chromosome 4p16.1, consisting of eight exons, encoding a transmembrane protein found in the endoplasmic reticulum which was named wolframin.[2,3] Wolframin is expressed in most cell types, and is particularly abundant in pancreatic β-cells, brain and heart.[28] In the eye, wolframin is mainly expressed in retinal ganglion cells, cells of the inner nuclear layer, photoreceptors and in glial cells of the proximal part of the optic nerve.[29,30] More than 200 different mutations of WFS1 gene have been identified in patients with Wolfram syndrome.[31]

A second gene has been identified in a small subset of patients, causing Wolfram syndrome 2, which includes serious gastrointestinal ulceration and bleeding but not diabetes insipidus. This gene, WFS2 (CISD2, 4q22-q24), which is responsible for Wolfram syndrome 2, encodes the endoplasmic reticulum intermembrane small protein (ERIS).[32]

The endoplasmic reticulum serves an important function in protein production, facilitating protein folding. Accumulation of misfolded and

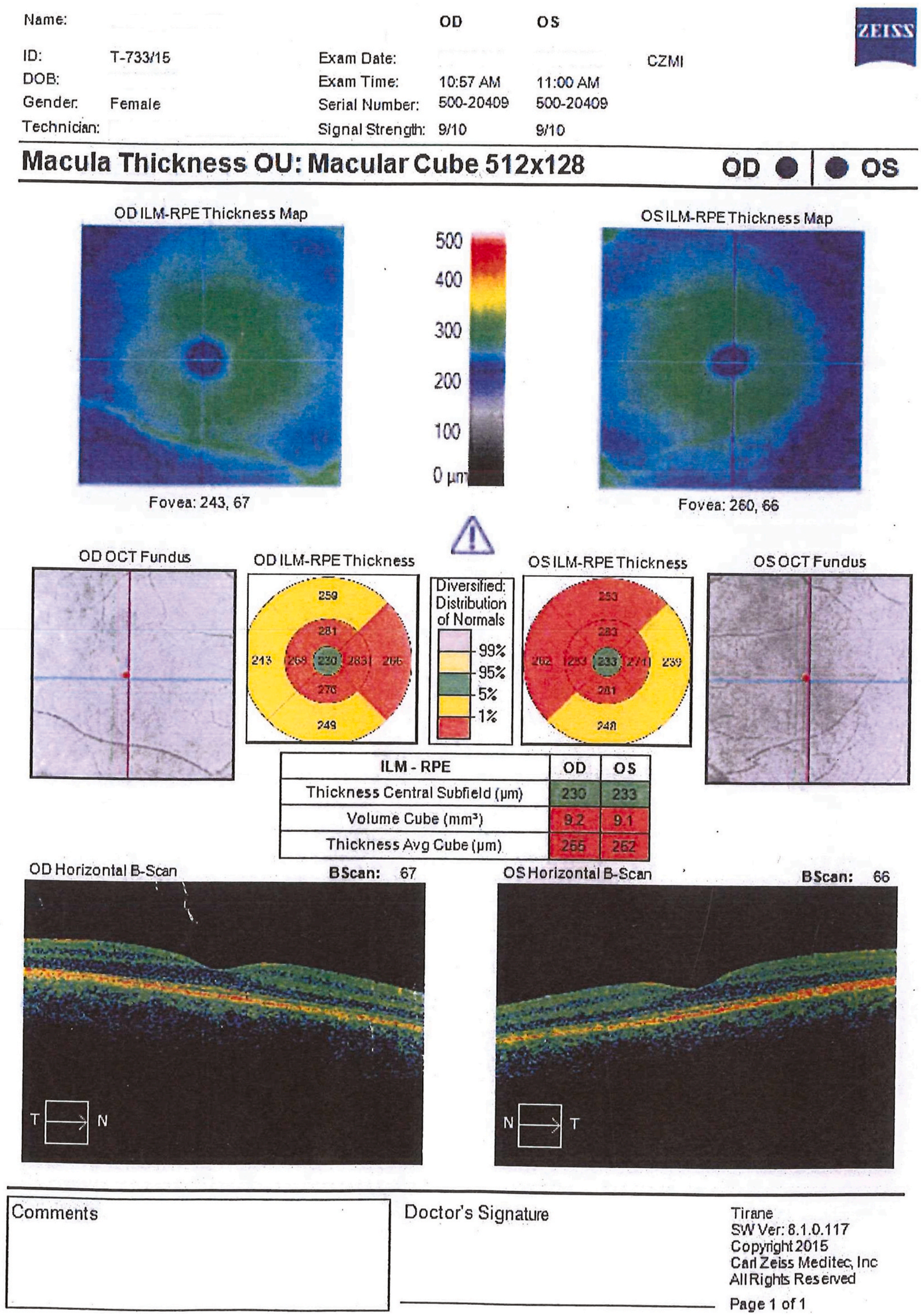

Fig. 4. Macular OCT scan with macular thickness map, both eyes.

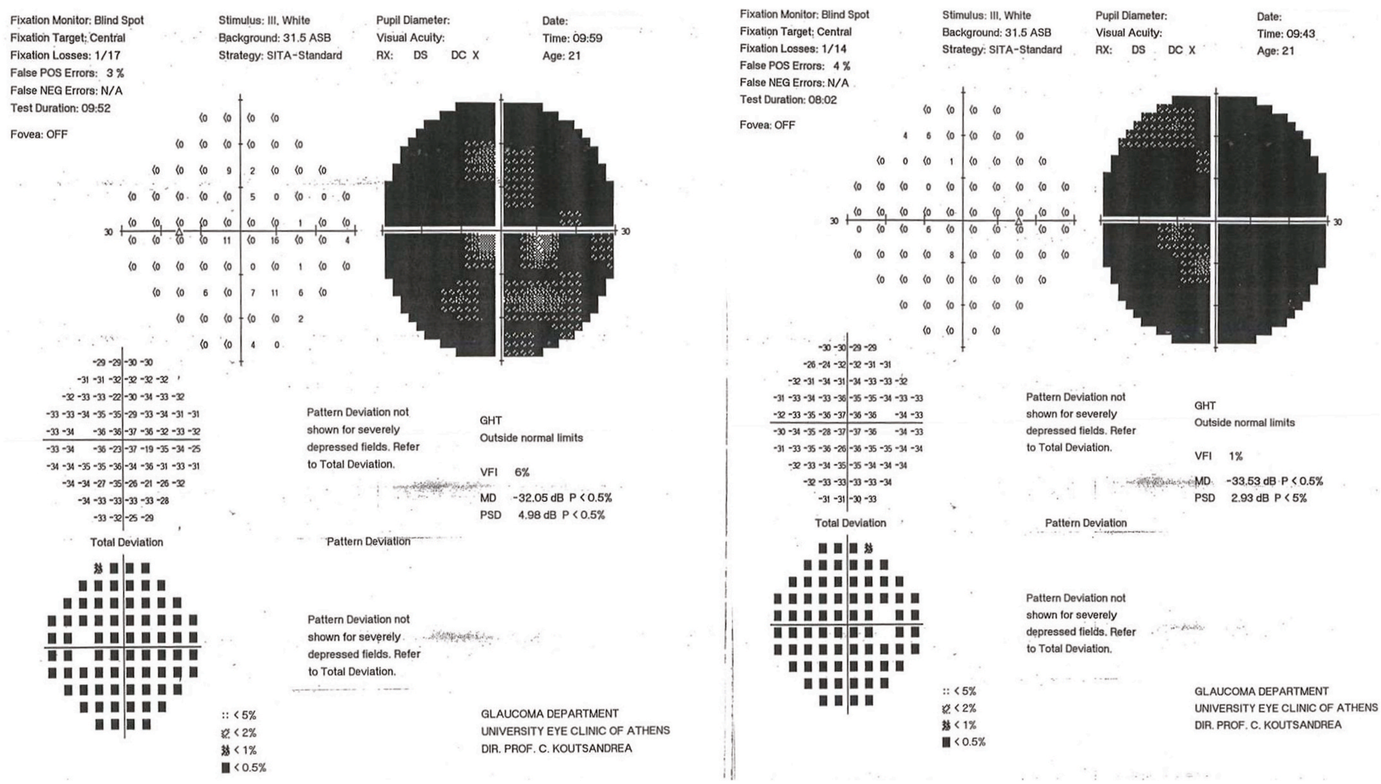

Fig. 5. Visual fields, both eyes.

unfolded proteins causes endoplasmic reticulum stress, which along with disruption of calcium homeostasis, both caused by dysfunctional Wolframin, is thought to be on the basis of Wolfram syndrome pathophysiology.[33]

3.2. Treatment - idebenone

No definitive treatment for Wolfram syndrome exists today. Treatment currently targets glycaemic control. Given the importance of ER stress and calcium homeostasis in the pathogenesis of the syndrome, it has been suggested that research focusing on these areas may result in slowing down or even halting the progression of cell death in Wolfram syndrome.4 Drug repurposing, the use of drugs already approved by regulatory agencies for other diseases, poses a viable and efficient option for treating WS.[4,34]

Meanwhile, the main field of research interest includes regenerative and gene therapy, with the aim being prevention of damage progression as well as replacement of damaged tissue such as pancreatic β-cells and retinal cells.[4,5]

Idebenone is a coenzyme Q10 derivative, with strong antioxidant properties, which has been used in the treatment of LHON.[35,36] The benefits of idebenone in LHON derive from both its antioxidant potency and from its ability to act as an electron carrier in the mitochondrial respiratory chain, thus ameliorating energy production in cellular level.[26–28,37] Inactive but viable retinal ganglion cells may benefit from energy restoration, hence some visual recovery may occur in patients with optic atrophy, with the use of idebenone.[38] Furthermore, studies have shown that inadequately myelinated axons may undergo occasional remyelination with the use of idebenone.[39]

Although optic atrophy in Wolfram syndrome is not pathophysiologically identical to that in LHON, mitochondrial dysfunction, alone or in the concept of ER-mitochondrial interaction, has been suggested to contribute in visual impairment in Wolfram syndrome.[12,40] The experimental use of idebenone in Wolfram syndrome may have resulted in some visual recovery, after six months of treatment.[41]

4. Conclusions

In this case, two siblings were referred with gradual bilateral vision loss and a presumed diagnosis of Leber's Hereditary Optic Neuropathy. Careful and detailed medical and family history led to appropriate testing which documented the diagnosis of Wolfram syndrome. Because of the rarity and clinical heterogeneity of WFS, the molecular genetic assay is essential to confirm the diagnosis and management of the WFS patients. To this day, there is no definite treatment for this disease, but the experimental use of idebenone has been suggested to improve visual function. Genetic testing of family members and offspring of patients is strongly recommended.

CRediT author statement

Tryfon Rotsos: Investigation, Writing - Original Draft, Writing - Review & Editing, Evangelia Papakonstantinou: Investigation, Writing - Original Draft, Chrysanthos Symeonidis: Writing - Review & Editing, Augoustinos Krassas: Resources, Smaragda Kamakari: Investigation, Writing - Original Draft.

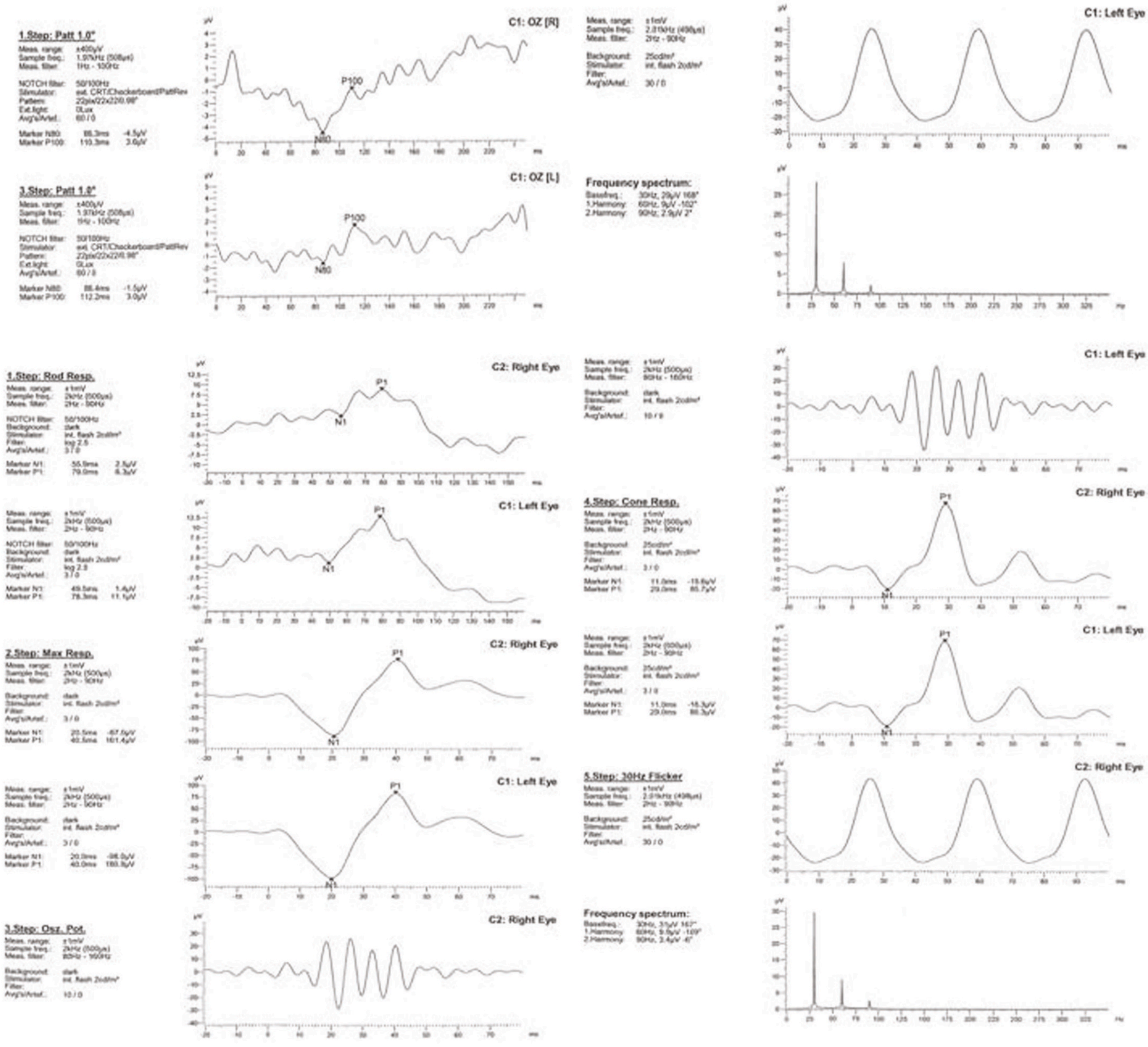

Fig. 6. Visual Evoked Potentials and Electroretigraphy, both eyes.

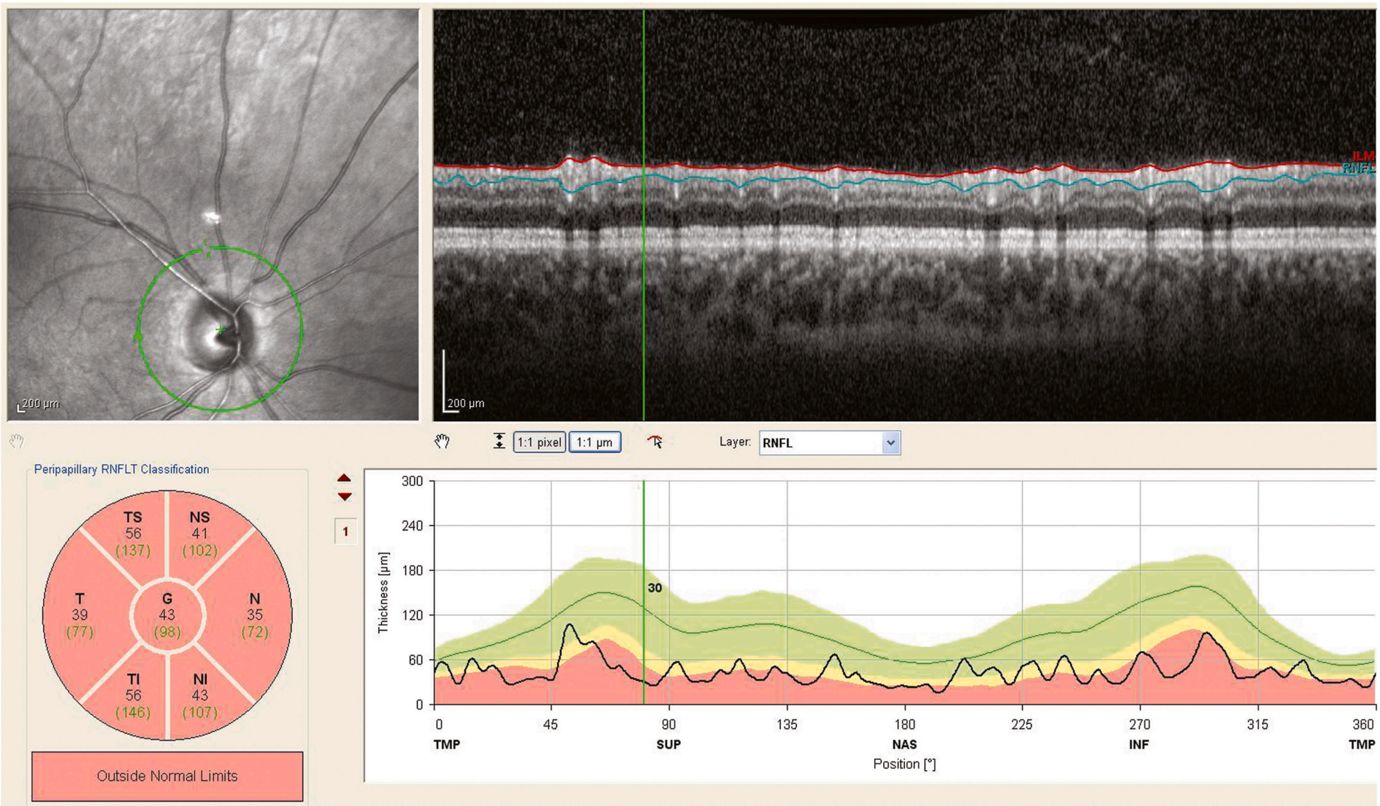

Fig. 7. OCT, RNFL thickness, Right Eye, Patient A.

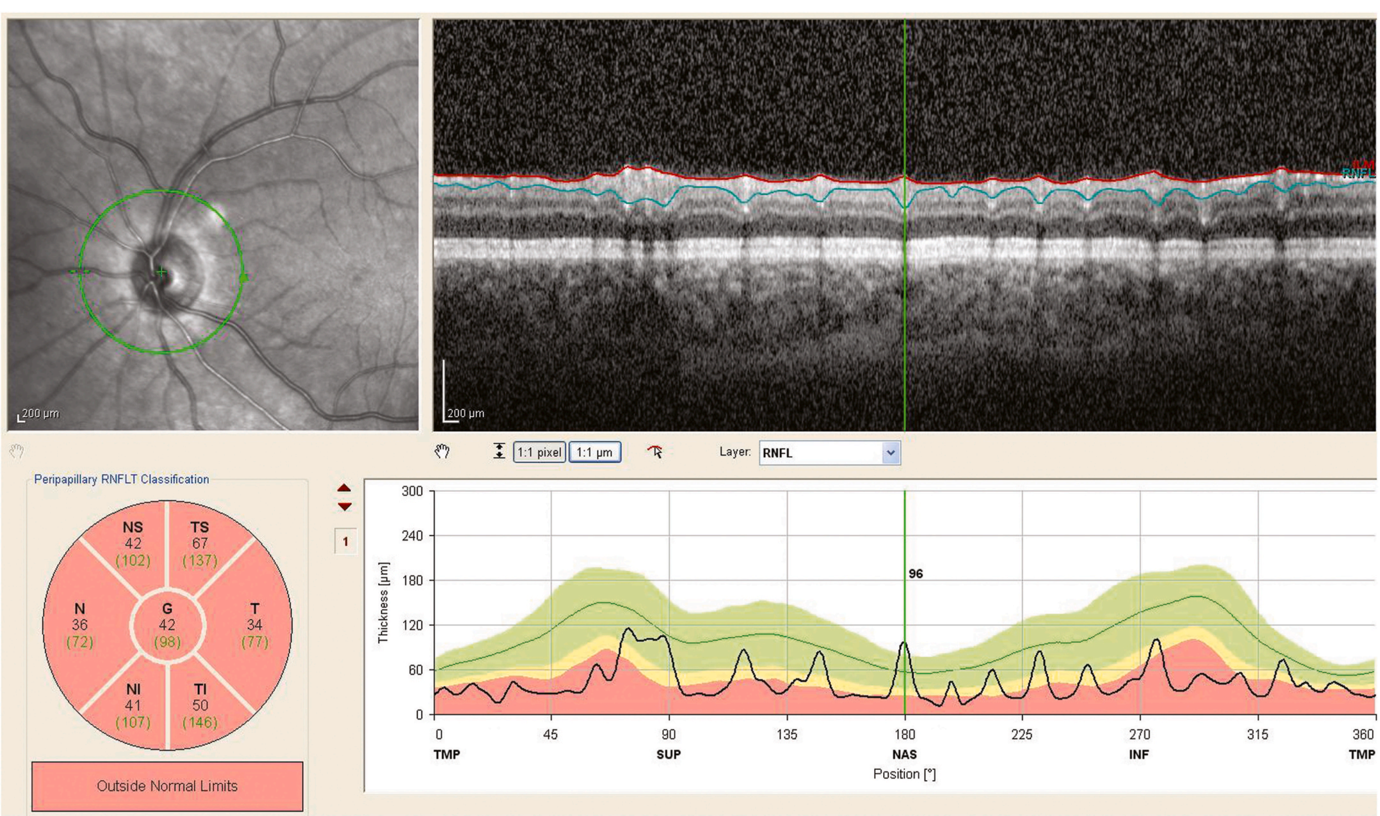

Fig. 8. OCT, RNFL thickness, Left Eye, Patient A.

Patient consent

Consent to publish this case report has been obtained from the patient in writing.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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