ARCHIVOS DE LA SOCIEDAD ESPAÑOLA DE OFTALMOLOGÍA

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Original article

Williams-Beuren syndrome case series with thinner fovea centralis and central corneal thicknesses

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ARTICLE INFO

Article history:
Received 3 February 2024
Accepted 12 November 2024
Available online 31 January 2025

Keywords:
Fovea
OCT
Williams-Beuren syndrome

ABSTRACT

Background/aims: To characterize the ocular signs of Williams-Beuren syndrome (WBS) in 3 cases examined at XXX University Ophthalmology Clinic.
Methods: Three patients with a diagnosis of WBS underwent comprehensive ophthalmic evaluation at the XXX University Ophthalmology, including best-corrected visual acuity, slitlamp biomicroscopy, dilated fundus examination, optical coherence tomography, corneal topography and colour fundus imaging.
Results: All 3 cases had decreased best corrected visual acuity, decreased ILM-RNFL thicknesses with a persistence of inner retinal layers on the SD-OCT examinations, decreased central corneal thickness yet normal epithelial thickness measurements and retinal arteriolar tortuosity in fundus examination.
Conclusion: WBS is a complex multisystem genetic disorder. The ocular findings observed in these cases which are decreased corneal thickness with normal epithelial thickness, decreased ILM-RPE thicknesses, and retinal arteriolar tortuosity may provide future insight into systemic vascular findings affected by a microdeletion of chromosome 7q11.23 which also contains elastin gene in WBS.

Serie de casos del síndrome de Williams-Beuren con disminución de la fóvea central y del espesor corneal central

Palabras clave:
Fóvea
OCT
Síndrome de Williams-Beuren

RESUMEN

Antecedentes/objetivos: Caracterizar las manifestaciones oculares del síndrome de Williams-Beuren (WBS) de tres casos que fueron examinados en la Clínica de Oftalmología de la Universidad XXX.

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https://doi.org/10.1016/j.oftale.2025.01.012

Métodos: Tres pacientes con un diagnóstico de SWB se sometieron a una evaluación oftálmica integral en la Universidad XXX de Oftalmología, que incluyó agudeza visual mejor corregida, biomicroscopía con lámpara de hendidura, examen del fondo de ojo dilatado, tomografía de coherencia óptica, topografía corneal e imágenes del fondo de ojo en color.
Resultados: Los 3 casos experimentaron un descenso de la agudeza visual mejor corregida, del grosor MLI-EPR con persistencia de las capas internas de la retina en los exámenes SD-OCT, un menor espesor corneal central y mediciones normales del espesor epitelial y tortuosidad arterial retiniana en el examen del fondo de ojo.
Conclusión: El SWB es un trastorno genético multisistémico complejo. Los hallazgos oculares observados en estos casos, que son un menor grosor corneal con un espesor epitelial normal, un menor grosor MLI-EPR y tortuosidad arterial retiniana podrían proporcionar información, en el futuro, sobre los hallazgos vasculares sistémicos afectados por una microdeleción del cromosoma 7q11.23, que también contiene el gen de la elastina en el SWB.

Introduction

Williams syndrome (WS) or Williams-Beuren syndrome (WBS) is a rare neurodevelopmental disorder resulting from the spontaneous deletion of genetic material in the chromosome 7 pair's q11.23 region, rendering individuals hemizygous for these specific genes. Typically spanning 1.5 up to 1.8 million base pairs and impacting around 28 genes, including the elastin gene (ELN), this deletion leads to symptoms characteristic of the condition.[1] The role of the elastin gene in preserving vessel, lung, and skin elasticity is crucial. It affects approximately 1 in every 7500 live births, equally distributed among males and females.[2] The syndrome exhibits a range of systemic changes, such as unique facial features (referred to as an "elfin face"), cardiovascular complications (most commonly supravalvular aortic stenosis), neurological and ophthalmological irregularities, connective tissue abnormalities, distinct personality traits, and infantile hypercalcemia.[3,4] Diagnosis primarily depends on clinical evaluation, but fluorescence in situ hybridization (FISH) helps confirm these genetic abnormalities.[5] The landmark study by Greenberg and Lewis identified several distinct characteristics in a significant cohort of WBS patients, including the stellate iris pattern, strabismus, situs inversus, and atypical branching of retinal vessels from the optic nerve.[6] This study aims to present and discuss the ocular examination findings from three cases of WBS observed at the XXX University ophthalmology department.

Methods

Three patients with a diagnosis of Williams-Beuren syndrome underwent comprehensive ophthalmic evaluation at the XXX University Ophthalmology, including best-corrected visual acuity, slit-lamp biomicroscopy, dilated fundus examination, optical coherence tomography, corneal topography and colour fundus imaging.

Case reports

Patient #1

A 17-year-old male diagnosed with WBS experienced a progressive vision decline in both eyes over 3 years. During the ophthalmic examination, the refractive error for the right eye measured +1.00 (–0.50 × 60), while for the left eye, emmetropia was recorded. His visual acuity, tested with the Snellen chart, was 0.5/0.9. In the biomicroscopic examination, the iris displayed a stellate pattern, a distinctive sign associated with WBS. The fundus examination revealed several loop-shaped, twisted vessels alongside normally appearing retinal vessels (Fig. 1A.1).

Spectral-domain optical coherence tomography (SD-OCT) confirmed the presence of mild foveal hypoplasia, displaying a persistence of inner retinal layers (Fig. 1A.2). Additionally, OCT angiography showed that abnormal vessels were not retinal vessels. Instead, they were consistent with prepapillary vascular loops. Measurements taken using SD-OCT indicated a central corneal thickness (CCT) of 486 μm for the right eye and 488 μm for the left eye (Fig. 1A.3). Meanwhile, the epithelial thickness (ET) maps showed normal readings. Notably, corneal topography appeared normal in this particular case.

Patient #2

An 11-year-old female patient was referred to the XXX University Ophthalmology Department. The ophthalmologic examination revealed a refractive error of +1.00 (–1.00 × 10) for the right eye and +1.25 (–0.75 × 155) for the left eye. The Snellen visual acuity test showed results of 0.7/0.7. During the biomicroscopic examination, the patient's iris exhibited a stellate pattern, a distinctive indicator of WBS. Fundus examination revealed increased vascular tortuosity (Fig. 2B.1). SD-OCT imaging displayed a widened foveal pit (Fig. 2B.2)

and a reduced ILM-RPE thickness. Notably, microperimetry, visual field, visual evoked potential (VEP) and electroretinogram (ERG) tests all exhibited normal results for the patient. The confirmed that foveal flattening did not correlate with any other macular disorder. Lastly, corneal topography revealed an irregular corneal surface and corneal thinning (Fig. 2B.3).

Patient #3

A 15-year-old male was examined at the XXX University Ophthalmology department. In the ophthalmologic examination, the patient's refractive error was –0.75 for both right and left eyes. The Snellen visual acuity test showed results of 0.7/0.7. No disease was observed during the biomicroscopic examination. However, increased vascular tortuosity was noted in

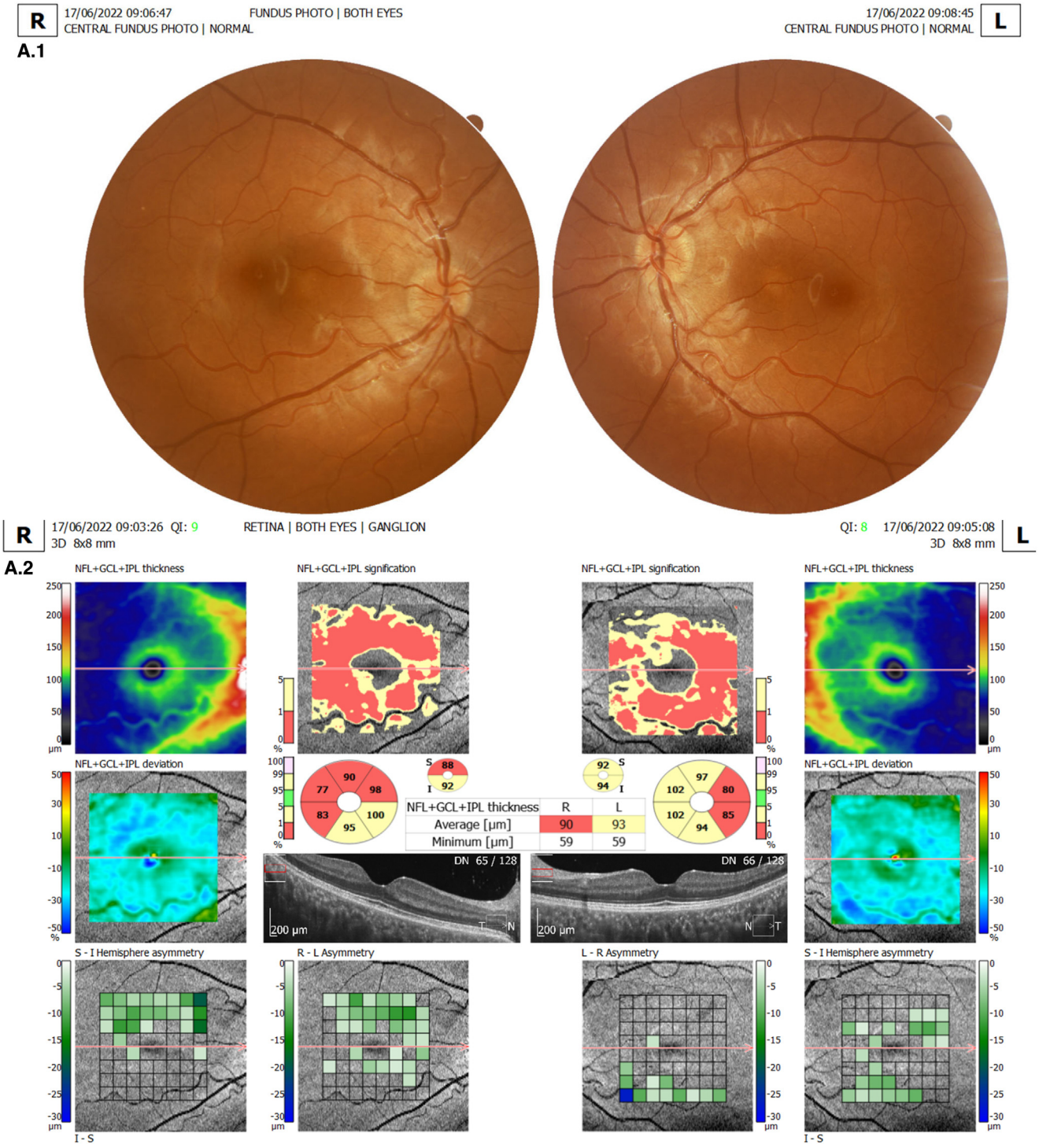
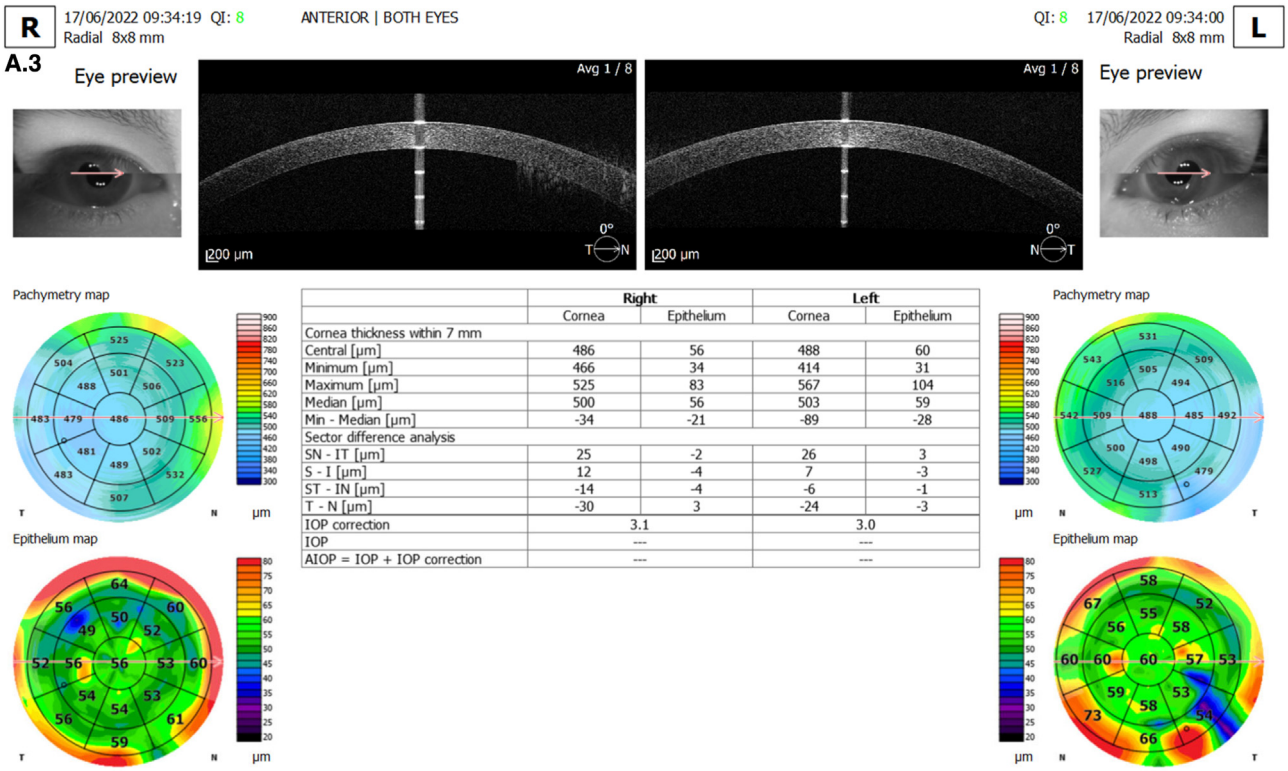


Fig. 1 – A1: Retinal vessel tortuosity. A2: OCT imaging showed broad foveal pit and thinning in NFL+GCL+IPL thickness. A3: Corneal pachymetry map showed corneal thinning.



	Right		Left	
	Cornea	Epithelium	Cornea	Epithelium
Cornea thickness within 7 mm				
Central [µm]	486	56	488	60
Minimum [µm]	466	34	414	31
Maximum [µm]	525	83	567	104
Median [µm]	500	56	503	59
Min - Median [µm]	-34	-21	-89	-28
Sector difference analysis				
SN - IT [µm]	25	-2	26	3
S - I [µm]	12	-4	7	-3
ST - IN [µm]	-14	-4	-6	-1
T - N [µm]	-30	3	-24	-3
IOP correction	3.1		3.0	
IOP	---		---	
AIOP = IOP + IOP correction	---		---	

Fig. 1 – *(Continued)*

the fundus examination. SD-OCT imaging displayed a flattened foveal curvature and thinning in the ILM-RPE thickness (Fig. 3C.1). Additionally, the SD-OCT optic nerve imaging indicated inferior RNFL thinning in both eyes (Fig. 3C.2). Central corneal thickness (CCT) measurements were recorded at 498 µm for both the right and left eyes (Fig. 3C.3), while corneal topography appeared normal.

Discussion

Williams syndrome (WBS) is a rare congenital disorder resulting from the deletion of a small segment of chromosome 7. This genetic condition presents a spectrum of developmental and medical challenges. Common signs associated with WBS include distinct facial characteristics, cardiovascular complications, intellectual disabilities with noticeable difficulties in social and language skills, hypersensitivity to sound, growth and developmental delays, hypercalcemia, an affable and outgoing personality, and potential musical and artistic abilities.[7–9]

Kuehlewein et al. provided significant insights into the ophthalmic findings associated with WBS. Their study highlighted a case of a 14-year-old Asian Indian girl who exhibited rod-cone dystrophy, offering a crucial link indicating that the genetic makeup of individuals with WBS can directly impact their vision.[10]

The study conducted by Weber et al. provided valuable insights into the ocular signs seen in individuals with WBS. Among the children examined, a significant 77% displayed refractive errors, with hyperopia and astigmatism being the most prevalent at 67% and 20%, respectively. Myopia was reported in 7% of cases, with only one reported instance of amblyopia. External features analysis revealed that 23% of the children exhibited epicanthus, and biomicroscopy identified 3 cases of stellate patterns in the irides. Strabismus was reported in 36.6% of patients, with esotropia being the dominant type at 82%. Additionally, binocular vision abnormalities were noted in 43% of patients, emphasizing the complexity of visual processing in this population. Funduscopy examinations further revealed diffuse arteriovenous tortuosity in 27% of cases, highlighting intricate vascular changes occurring in individuals with WBS.[4]

In our cases, the visual acuities did not reach 10/10 in any of them, and the precise reasons remain unclear. In patients #1 and #2, the decrease in visual acuity could be attributed to mixed astigmatism, albeit not highly anisometropic. However, patient #3 exhibited simple myopia only. Another potential contributor to this decrease might be the thinning of the retinal nerve fiber layer (RNFL), although this couldn't be confirmed through microperimetry, visual field, VEP, or ERG tests. Notably, in patient #2, a notably broad foveal pit was observed, a finding that remains unexplained. Interestingly, Huryn et al. also identified this phenomenon in one-third of the patients in their case series.[11]

Absolutely, the collective information from these studies—combined with our own findings—highlights the extensive spectrum of ocular WBS-related abnormalities. It underscores the critical need for comprehensive and meticulous ophthalmic assessments in individuals diagnosed with WBS. Understanding and addressing these ocular manifesta-

tions are pivotal in offering comprehensive care and support to individuals living with WBS.

Conclusions

In conclusion, the data presented in our study underscores the broad spectrum of ocular abnormalities associated with WBS. Ophthalmologists should keep in mind the potential association with WBS when they come across cases exhibiting flattened or broad foveal pits, as well as decreased RNFL thickness, particularly if these ocular findings are accompanied by the distinctive facial features characteristic of WBS. These instances highlight the importance of conducting thorough ophthalmic evaluations for individuals affected by WBS. The presentation of such cases can facilitate earlier and more straightforward identification of WBS cases, aiding researchers and healthcare professionals in providing timely and appropriate care.

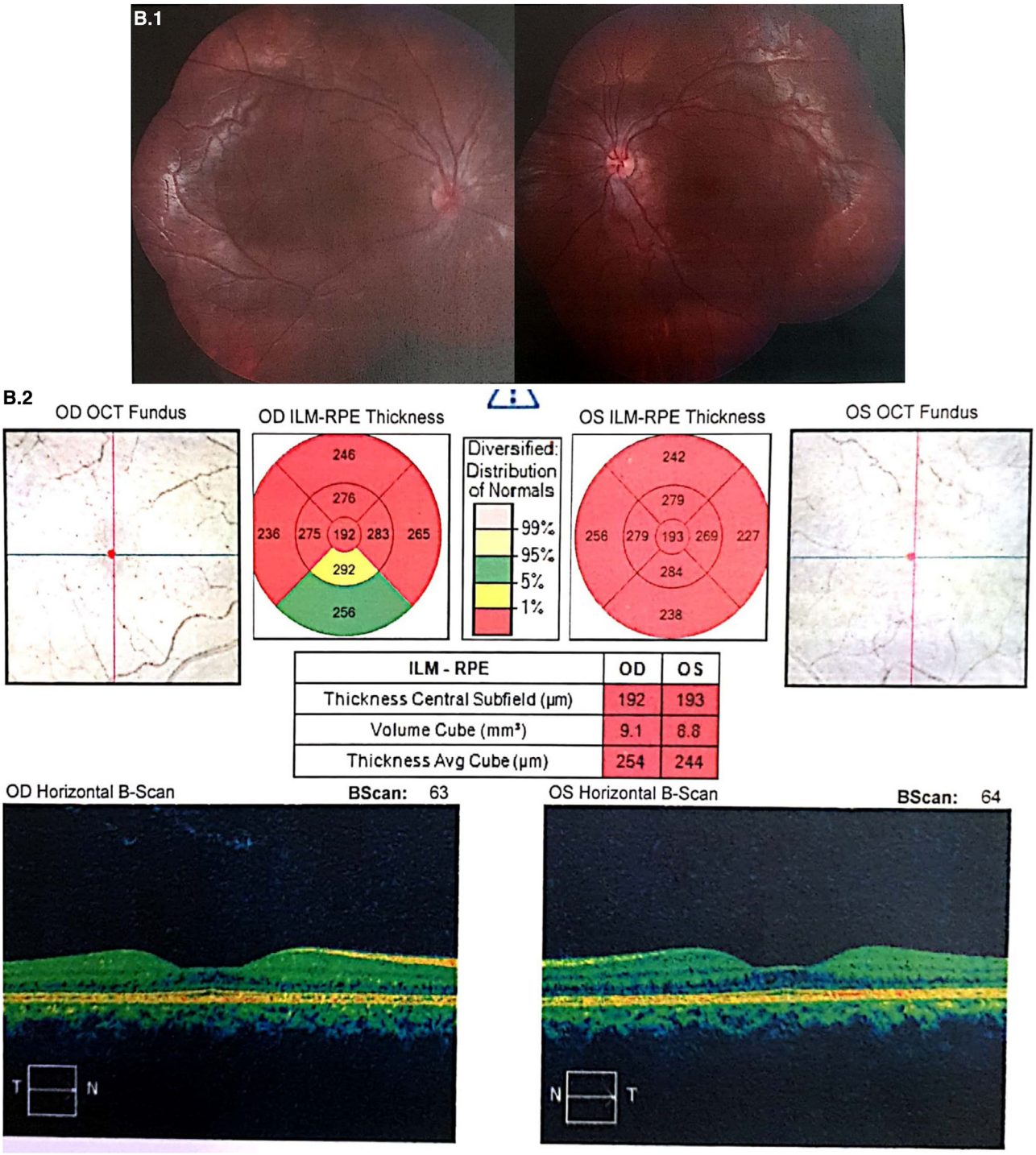


Fig. 2 – B1: Retinal vessel tortuosity. B2: The OCT imaging revealed a broadened foveal curvature and a reduction in ILM-RPE thickness. B3: The corneal topography showed an irregular corneal surface and corneal thinning.

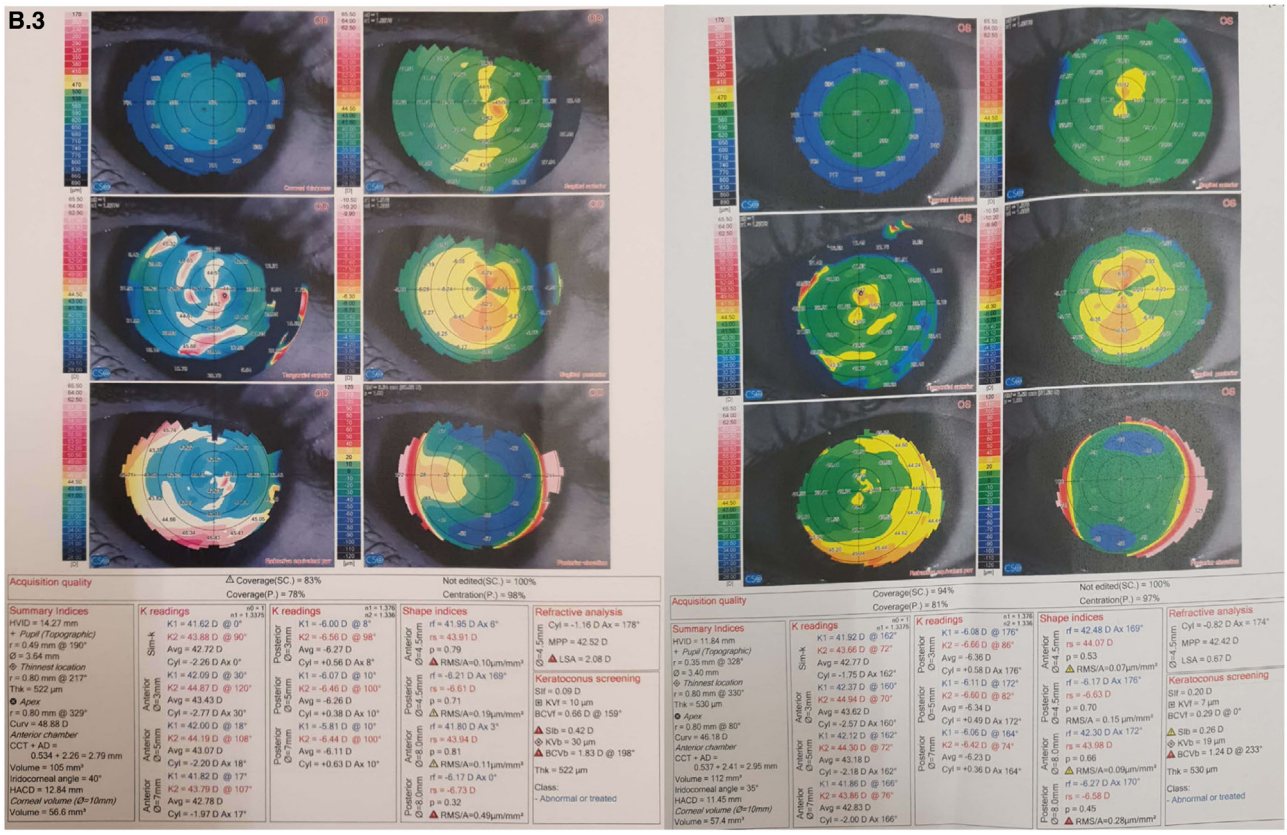


Fig. 2 – (*Continued*)

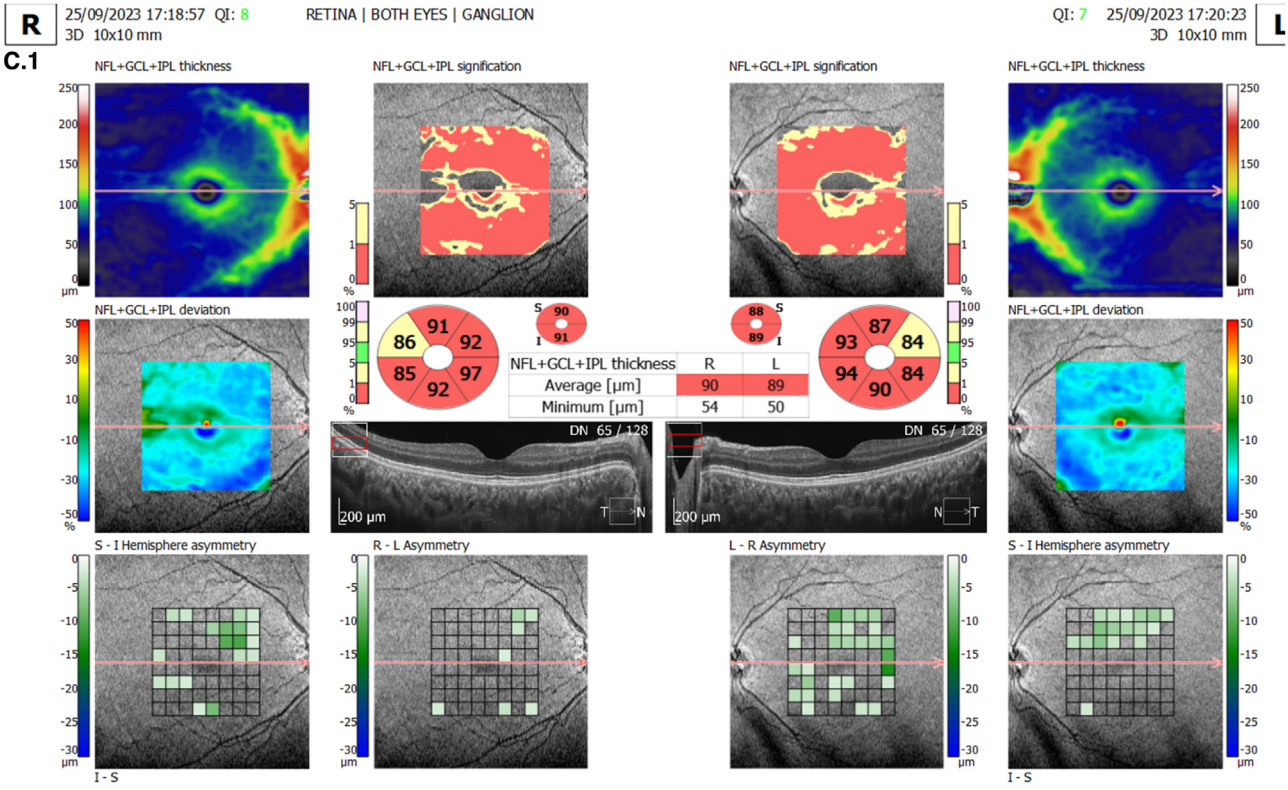


Fig. 3 – C1: OCT imaging showed flattened foveal curvature and thinning in NFL + GCL + IPL thickness. C2: RNFL thickness map showing inferior thinning. C3: Corneal pachymetry map showed corneal thinning.

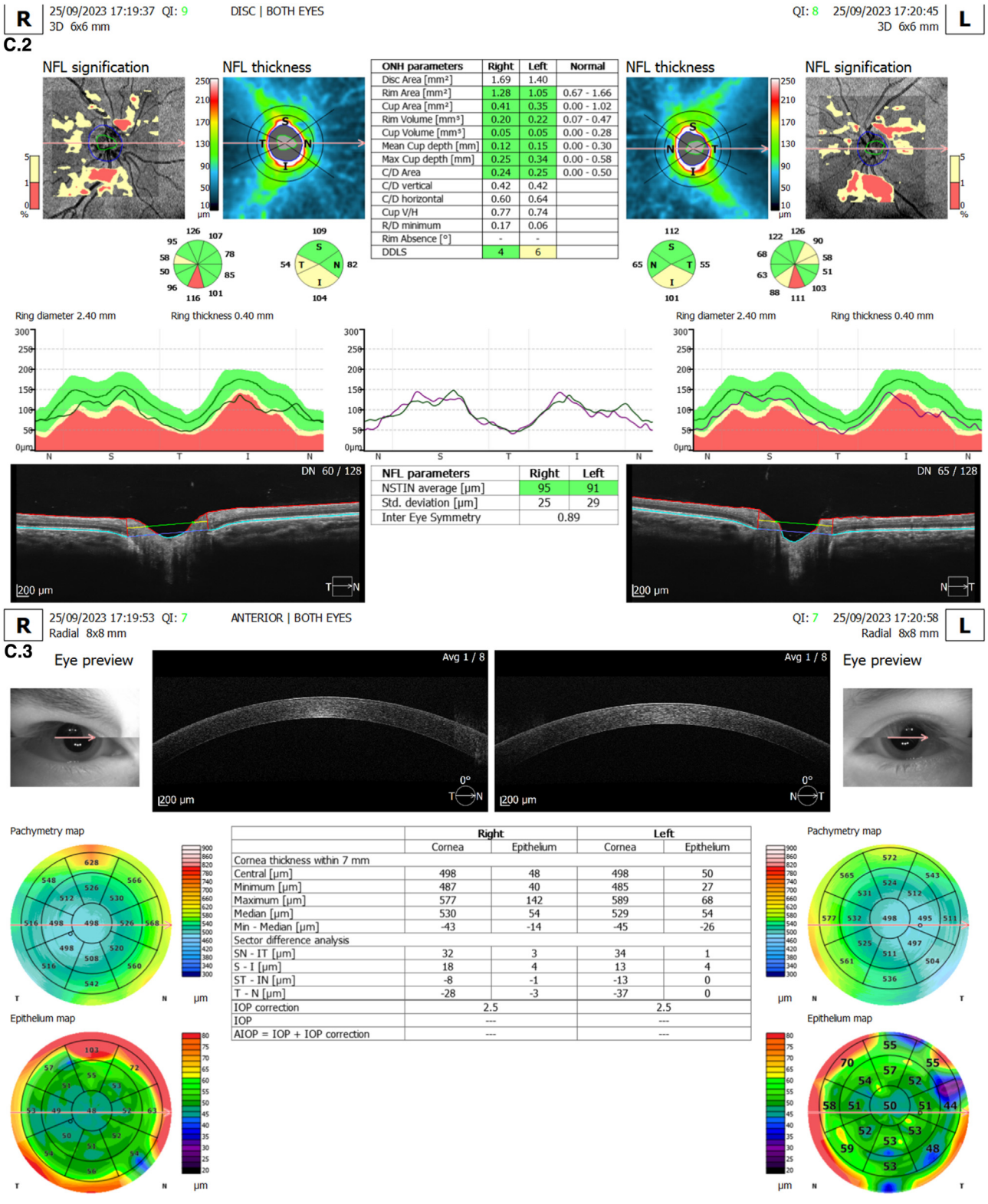


Fig. 3 – (*Continued*)

Ethical considerations

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

IRB approval was obtained

Written consent to publish potentially identifying information, such as details or the case and photographs, was obtained from the patient(s) or their legal guardian(s).

Funding

None declared.

Declaration of competing interest

None declared.

Acknowledgements

The authors alone are responsible for the content and writing of the paper.

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