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NEW OPHTHALMIC ABNORMALITIES IN AN ADULT PATIENT WITH WILLIAMS SYNDROME. A CASE REPORT

Keywords: Esotropia; Anterior Capsule of the Lens; Astigmatism; Williams Syndrome.
Palabras clave: Esotropía; Cápsula Anterior del Cristalino; Astigmatismo; Síndrome de Williams.

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ABSTRACT

Introduction: Williams syndrome is a genetic disorder caused by a microdeletion on chromosome 7q11.23, which may manifest with various systemic and ophthalmic symptoms. Children with this syndrome present with visual alterations such as strabismus, keratoconus, and amblyopia. Infantile esotropia, dissociated vertical deviation, and oblique muscle weakness of the eye are among the documented forms of strabismus. However, further research is needed to better understand ophthalmologic manifestations in individuals with this syndrome.
Case presentation: A 34-year-old man attended an ophthalmology consultation at a clinic in Istanbul, Turkey, in 2023 after experiencing visual and spatial perception difficulties over the previous month. Fluorescence in situ hybridization (FISH) confirmed a diagnosis of Williams syndrome reported in his medical history. Genetic analysis revealed a deletion in the elastin gene (*ELN*), located at 7q11.23 (*ELN*×1), with two normal signals detected at 7q22 (*ELN*×2). As part of the ophthalmologic examination, an autorefractometer was used to measure refractive error in both eyes. Imaging studies were also performed using the IOL Master 700 to assess anterior segment parameters, as well as optical coherence tomography (OCT) using the 3D OCT-2000 to assess the retina. The findings of this study suggested that the patient had specific ocular alterations that significantly affected his visual function, which were associated with Williams syndrome. Reduced visual acuity (0.4 in both eyes) was observed, probably related to astigmatism of primarily lenticular origin and a shallow anterior chamber, indicating that the syndrome affected the development of the anterior segment of the eye.
Conclusion: Williams Syndrome plays an important role in the development of astigmatism. A very shallow anterior chamber depth, along with a high degree of lenticular astigmatism, suggests that this syndrome significantly affects the lens, which is related to the ocular developmental disorder characteristic of this condition. A thorough ophthalmologic examination from childhood onwards is advised in patients with Williams syndrome to identify and treat any ocular problems in a timely manner, given its potential impact on visual function.

RESUMEN

Introducción. El síndrome de Williams es un trastorno genético causado por una microdeleción en el cromosoma 7q11.23. Se caracteriza por una variedad de síntomas sistémicos y oculares, y en niños con este trastorno se han identificado alteraciones visuales como estrabismo, queratocono y ambliopía. Entre las formas documentadas de estrabismo se encuentran esotropía infantil, desviación vertical disociada y debilidad de los músculos oblicuos del ojo. Sin embargo, se requiere de más investigación para comprender mejor las manifestaciones oftalmológicas en personas con esta condición.

Presentación del caso. Hombre de 34 años que en 2023 acudió a consulta oftalmológica en una clínica de Estambul, Turquía, tras experimentar problemas de percepción visual y espacial durante el último mes. La técnica de hibridación fluorescente *in situ* (FISH, por su sigla en inglés) confirmó un diagnóstico de síndrome de Williams registrado en su historia clínica. El análisis genético reveló una deleción en el gen de la elastina (*ELN*), localizado en 7q11.23 (ELN×1), con dos señales normales detectadas en 7q22 (ELN×2). Como parte del examen oftalmológico, se utilizó un autorrefractómetro para medir el error refractivo en ambos ojos. Además, se realizaron estudios de imagen con el dispositivo IOL Master 700 para evaluar los parámetros del segmento anterior, y tomografía de coherencia óptica (OCT, por su sigla en inglés) con el equipo 3D OCT-2000 para valorar la retina. Los hallazgos de este estudio sugirieron que el paciente presentaba alteraciones oculares específicas que afectaban de forma significativa la función visual, asociadas al síndrome de Williams. Se observó una agudeza visual reducida (0.4 en ambos ojos), probablemente relacionada con astigmatismo de origen principalmente lenticular y una cámara anterior poco profunda, lo que indicó que el síndrome afectaba el desarrollo del segmento anterior del ojo.
Conclusión. El síndrome de Williams desempeña un papel importante en el desarrollo del astigmatismo. Una profundidad de cámara anterior muy reducida, junto con un alto grado de astigmatismo lenticular, sugiere que este síndrome afecta significativamente el cristalino, lo cual está relacionado con el trastorno del desarrollo ocular característico de esta condición. Se recomienda realizar un examen oftalmológico completo desde la infancia en pacientes con síndrome de Williams para identificar y tratar oportunamente cualquier alteración ocular dado el posible impacto sobre la función visual.

INTRODUCTION

Williams syndrome (WS) is a rare genetic disorder first identified in 1993 through fluorescence in situ hybridization (FISH), which revealed a deletion of one allele of the *ELN* gene on chromosome 7q (1). It is now well established that WS results from a microdeletion at chromosome 7q11.23 (1,2) and has an estimated incidence at birth of approximately 1 in 20 000 live births (2,3).

This genetic syndrome is caused by a hemizygous deletion involving at least 28 genes (2-6), and the reduced expression of several key genes (*CLIP2, GTF2I, GTF2IRD1,* and *LIMK1*) contributes to its characteristic clinical phenotype, which includes abnormalities in neural and retinal development, as well as visuospatial processing deficits (3-6). In addition to these effects, the reduced expression of these genes has also been associated with cardiovascular abnormalities, retinal changes, specific motor and cognitive deficits, neurobehavioral profiles, and craniofacial features (3-8). Ocular findings in individuals with WS include

strabismus (29-78%), with esotropia (59%), oblique muscle dysfunction (53%), and dissociated vertical deviation (37%) being the most common, as well as amblyopia (32%), cataract (1.97%), and ptosis (1.32%) (9). More recently, an association with keratoconus was also identified (10), although further research is needed, particularly in adult patients.

Visual memory is defined as the ability to store visual information from the visual field into memory and, subsequently, retrieve or discard it. Individuals with WS often exhibit average IQ scores of approximately 55, indicating mild to moderate intellectual disability. However, facial memory and language abilities are generally better preserved compared to skills such as drawing, visuospatial memory, and numerical processing (11). Visual disorders significantly influence the development of children and individuals with neurodevelopmental disorders, affecting numerous functional skills and their capacity to engage in daily activities (12). Ophthalmic disorders resulting from developmental disorders may impair visual function.

The following is the case of a patient with WS who exhibited visuomotor dysfunction associated with shallow anterior chamber depth (ACD), high corneal and lenticular astigmatism, curved crystalline lens, reduced white-to-white (WTW) corneal diameter, atypical flattening of the posterior fovea, multiple retinal anomalies, and visual acuity of 0.4 logMAR.

CASE PRESENTATION

A 34-year-old male patient presented to an ophthalmology clinic in Istanbul, Turkey, in 2023, due to persistent visual and spatial perception difficulties persisting for one month. His medical history reported a diagnosis of WS at six months of age, as well as genetic testing performed during his adolescence. The FISH test showed a deletion in the elastin gene (*ELN*) located at 7q11.23 (*ELN*×1), with two normal signals detected at 7q22 (*ELN*×2), findings consistent with WS. The patient had a history of aortic stenosis, previously assessed by cardiology, and neurogenic bladder evaluated by nephrology.

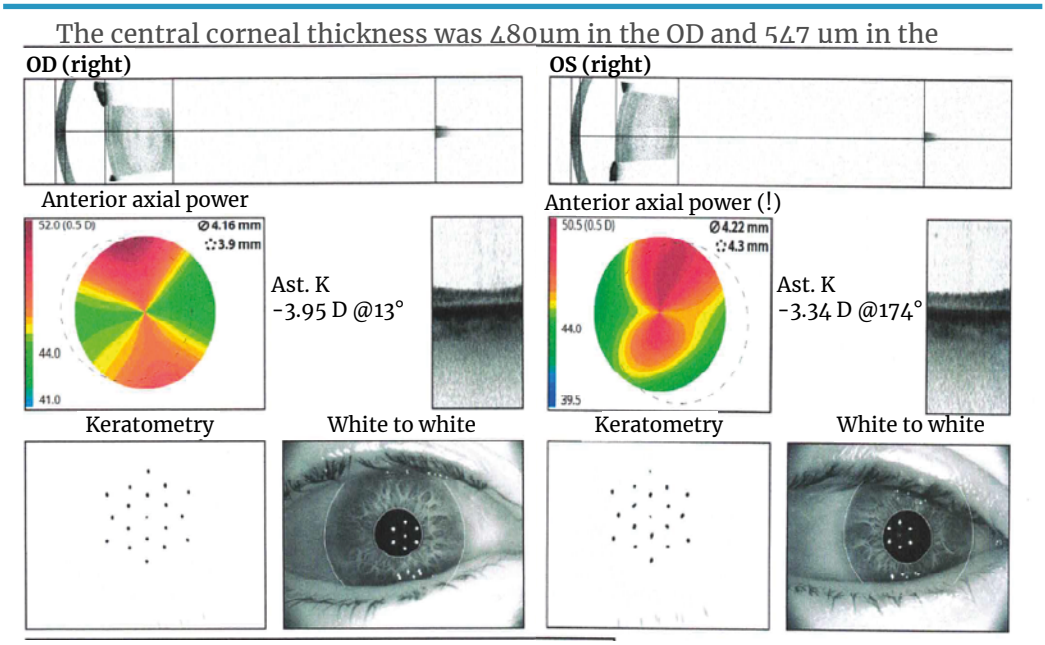
Regarding development, he did not acquire writing or drawing skills until the age of seven. After receiving special education until age 15, he engaged in activities such as writing and painting, although his reading level remained at the primary school grade, and despite his learning difficulties, he was socially dependent on his parents. Over the last ten years, he had experienced anxiety, which was effectively treated with antipsychotic medication. Although his writing and drawing skills improved with education, he recently showed a decline in these areas, along with episodes of irritability. The family sought evaluation suspecting progression of long-standing myopia, present since age five, as a potential cause of these symptoms.

During the consultation, a typical WS facial phenotype was observed, including a characteristic forehead and speech impairments. The patient

demonstrated good auditory rote memory and could follow commands, although he often had difficulty articulating words and phrases. He retained the ability to recognize individuals that he had recently met over extended periods, but his visual memory, previously strong, had reportedly declined. Emotional connections enhanced his ability to recognize people, whereas recall of objects was impaired. The patient's mother reported episodes of the patient misplacing his belongings and failing to recognize them as his own. During examination, the patient was able to comply only with basic instructions.

Refraction was measured in both eyes using a Plusoptix® A09 autorefractometer. As part of a comprehensive ophthalmologic evaluation, retinal imaging was performed with a 3D OCT-2000 optical coherence tomography device, and anterior segment parameters were assessed using an IOL Master 700. Regarding refraction, it was found that refractive error was +0.75 (-6.25×176) for the right eye (OD) and +0.25 (-5.75×165) for the left eye (OS), indicating high astigmatism in both eyes. As for ocular biometry, the ACD was very shallow in both eyes, with values of 2.85mm in the OD and 2.82mm in the OS. The biometric measurements showed that the axial length of both eyes was within the normal range, with 22.60mm in both eyes. Additionally, a reduction in the WTW diameter was observed, with measurements of 11.4mm in the OD and 11.3mm in the OS, which are below average (Figure 1).

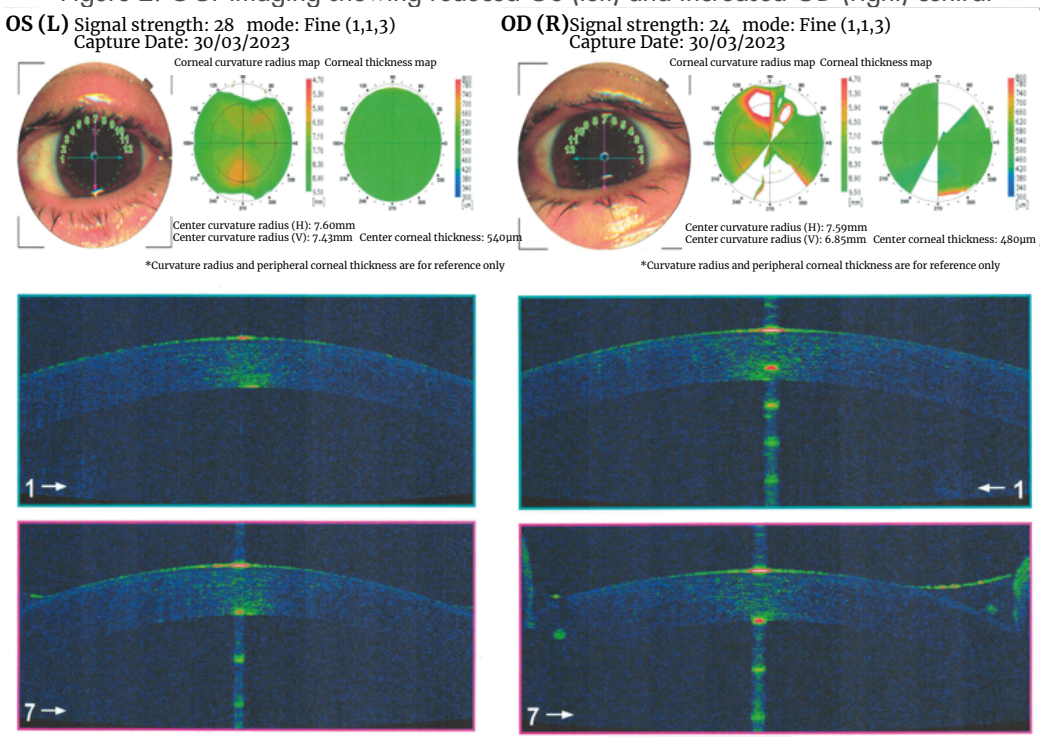
Figure 1. IOL imaging showing biometric values of OD (right) and OS (left) eyes.
Source: Own elaboration.



The central corneal thickness was 480um in the OD and 547 um in the OS (Figure 2). Although both values are within clinically acceptable ranges,

a significant asymmetry was observed between the eyes (OD shows relative thinning compared to the population average (~530µm)). Interpupillary distance was 61mm, which is within normal limits despite the characteristic facial expression associated with WS.

Figure 2. OCT imaging showing reduced OS (left) and increased OD (right) central



corneal thickness with flattening fovea.
Source: Own elaboration.

Refractive parameters, including corneal and total astigmatism, were measured with the IOL Master 700 and Plusoptix® A09. Flat keratometry for the OS (K1) was 44.11 D, while steep keratometry (K2) was 48.06 D. The OD had flat keratometry (K1) at 45.46 D and steep keratometry (K2) at 48.80 D (Figure 2). This demonstrated elevated corneal astigmatism (>0.75 D), with 3.95 D in the OD. However, the total refraction obtained by autorefraction was lower than the estimated value, suggesting a significant lenticular component. This finding suggested a substantial involvement of the lens in the generation of astigmatism, attributable to developmental ocular abnormalities associated with WS.

Posterior segment OCT revealed structural macular abnormalities in both eyes, consisting of foveal flattening, attenuation of the foveal pit, and a

hypoplastic appearance, with an average macular thickness of 242.6µm and central thickness of 193µm (Figure 3). These findings were symmetrical in both eyes. Binocular visual acuity was 0.4 on the Snellen scale.

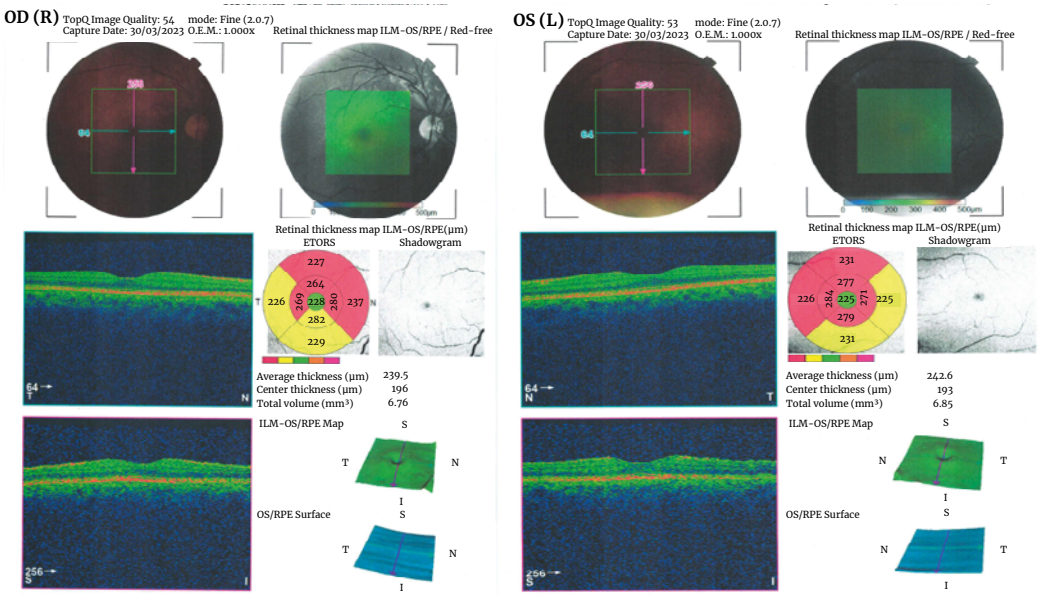


Figure 3. OCT imaging showing reduced OS (left) and increased OD (right) central retinal thickness.

Source: Own elaboration.

The findings suggest that WS may significantly contribute to the development of refractive errors, particularly astigmatism. A markedly reduced ACD, together with a high degree of lenticular astigmatism, indicate that this syndrome significantly affects the lens, which is related to the ocular developmental disorder characteristic of WS.

DISCUSSION

Few studies have explored the possible correlation between the severity of ophthalmic manifestations in WS. Lee *et al.* (13) reported a deletion of the *ELN* gene at the 7q11.23 locus in two clinical cases presenting with myopic astigmatism and 8-prism diopter esotropia. Both patients exhibited a star-shaped iris pattern, oval-shaped pupils, and increased retinal vascular folds. Similarly, the patient evaluated in this study presented with high astigmatism (up to -6.25 D) and structural retinal abnormalities, including foveal flattening and foveal hypoplasia. These findings support the association between *ELN* gene deletion and a complex ocular phenotype.

Although Todorova *et al.* (9) considered the association between a 7q11.23 microdeletion and features such as unilateral microphthalmia and anterior segment dysgenesis unlikely, the biometric findings observed in this case —including a reduced ACD and a below-average WTW corneal diameter— support the possibility that this deletion may indeed affect the development of the anterior segment, even in the absence of overt dysgenesis. Castelo *et al.* (14) also highlighted the association between visual abnormalities and both ocular and cerebral structural anomalies in patients with WS, suggesting a more complex and systemic visual phenotype.

A study conducted by Huryn *et al.* (15) in a cohort of 57 patients with WS reported that retinal arteriolar tortuosity may serve as an ophthalmic marker, with potential implications for systemic vascular involvement in this syndrome. Although arteriolar tortuosity was not observed in the present case, having evidence of structural retinal anomalies, such as foveal flattening and hypoplasia, suggests abnormal retinal development. Within the context of a multisystemic disorder such as WS, these findings further support the interrelation between ocular and systemic manifestations.

Castelo *et al.* (14) also demonstrated that reduced retinal thickness, abnormal optic disc concavity, and impaired visual responses in patients with WS may be associated with visuospatial deficits. In line with these findings, the present case exhibited atypical foveal flattening, a finding that was also described by Demirci *et al.* (16) in a pediatric patient with WS. However, unlike those previous reports, our results suggest that these structural alterations may not only persist but also progress into adulthood.

The findings of this study support the existence of specific ocular alterations in WS that significantly impact visual function. The patient examined exhibited reduced visual acuity (0.4 in both eyes), likely related to predominantly lenticular astigmatism, as well as decreased ACD, indicating impaired development of the anterior segment of the eye. These refractive and anatomical features reflect the involvement of the lens and other ocular structures as part of the clinical phenotype of the syndrome. Therefore, early and regular ophthalmologic follow-up is essential in these patients to ensure timely detection and appropriate management of associated visual impairments.

CONCLUSION

WS is a rare disorder that may present multiple genetic alterations. In order to better understand the condition, this study analyzed both the ophthalmic and genetic features associated with WS. In addition to the well-documented cardiovascular and renal findings, the results highlight the importance of incorporating detailed ophthalmologic evaluations into the clinical assessment of patients with WS,

particularly in pediatric cases. Early detection of ophthalmic manifestations is essential for the timely management of visual complications and should be considered a routine component of care in individuals diagnosed with WS.

ETHICAL CONSIDERATIONS

Informed consent was obtained from the patient in order to prepare this case report. The center's protocols for the diagnosis and handling of patient data were followed for publication purposes.

CONFLICT OF INTEREST

None stated by the authors.

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