

Keratoconus associated with Williams-Beuren syndrome: a new case report

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Dear Editor,

I am Dr. Soraya Mediero, from Department of Ophthalmology of La Paz University Hospital, Madrid, Spain. I write to present a case report of keratoconus associated with Williams-Beuren syndrome (WBS). To our knowledge, this is the fourth report of keratoconus associated with WBS and the first case to be treated with transepithelial cross-linking and corneal segments. And to our knowledge, such a case of WBS associated with megalopapilla has not been previously reported in the literature.

INTRODUCTION

WBS is a rare genomic multisystem disorder with a prevalence of 1:7500 to 1:10 000^[1]. WBS is caused by the contiguous deletion of 26-28 genes, including the elastin gene at 7q11.23^[2-3]. Sporadic inheritance is the most common pattern for this disease^[4], and symptoms typically include dysmorphic facial features, intellectual disability, cardiovascular disease, infantile hypercalcemia, connective tissue disorders and distinctive personality characteristics^[5-6].

The ophthalmologic features described in WBS affect the anterior and posterior segment of the eye and include iris stromal hypoplasia, a clear stellate pattern in the iris, strabismus (usually esotropia and hyperopia), ptosis, congenital cataracts, Marcus-Gunn phenomenon, reduced stereoacuity and retinal vascular tortuosity^[2,4]. The optic nerve is exceptionally affected by this syndrome and can suffer disc hypoplasia and increased disc excavation^[2].

Keratoconus is a fairly common bilateral, non inflammatory, degenerative axial ectatic condition of the cornea that progresses

to corneal thinning, increasingly irregular astigmatism and the onset of corneal opacities^[4]. The prevalence of keratoconus in the general population ranges from 8.8 to 54.4 per 100 000 inhabitants^[7], but its association with WBS is very rare. In fact, the case of keratoconus reported below is the fourth associated with WBS reported to date.

CASE REPORT

A 23-year-old man was referred to our center 3y ago due to a progressive decline in visual acuity over 2y. He had been diagnosed with WBS by deletion of chromosome 7q11.23 at the age of 5 years, initially suspected by the pediatric neurologist, and subsequently confirmed by fluorescent *in situ* hybridisation (FISH) analysis with the elastin Williams syndrome chromosome region (WSCR) probe (Oncor[®]). The patient presented dysmorphic facial features and mild intellectual disability, but there were no associated connective tissue disorders. At that time, his uncorrected visual acuity was 20/20 in the right eye (RE) and 20/400 in the left eye (LE), and the best spectacle-corrected visual acuity was 20/60 in the LE. Refraction was -1.25/-2.00×67 in the RE and -9.25/-13.00×154 in the LE. The slit-lamp examination showed no abnormalities in the RE; however, the LE cornea showed a Fleischer's iron ring and Vogt's striae. The iris, lens and pupillary reaction were normal. The intraocular pressure measured with Goldmann tonometer was 12 mm Hg in the RE and 8 mm Hg in the LE. Ultrasonic pachymetry showed a central corneal thickness of 433 µm in the RE and 345 µm in the LE.

Funduscopy revealed a megalopapilla with a vertical diameter of 2.72 mm, a vertical cup-to-disc ratio of 0.8 in the RE (Figure 1)

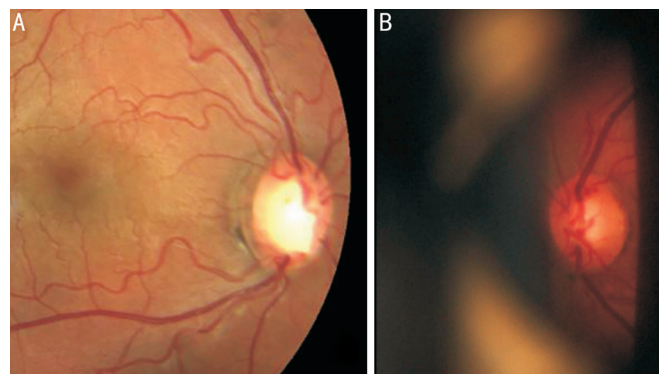


Figure 1 Retinography A: RE funduscopy showing vascular tortuosity and megalopapilla; B: LE funduscopy showing normal size papilla. Photo taken with central mirror of Goldmann lens because of low quality imaging with regular retinography due to anterior segment disorder.

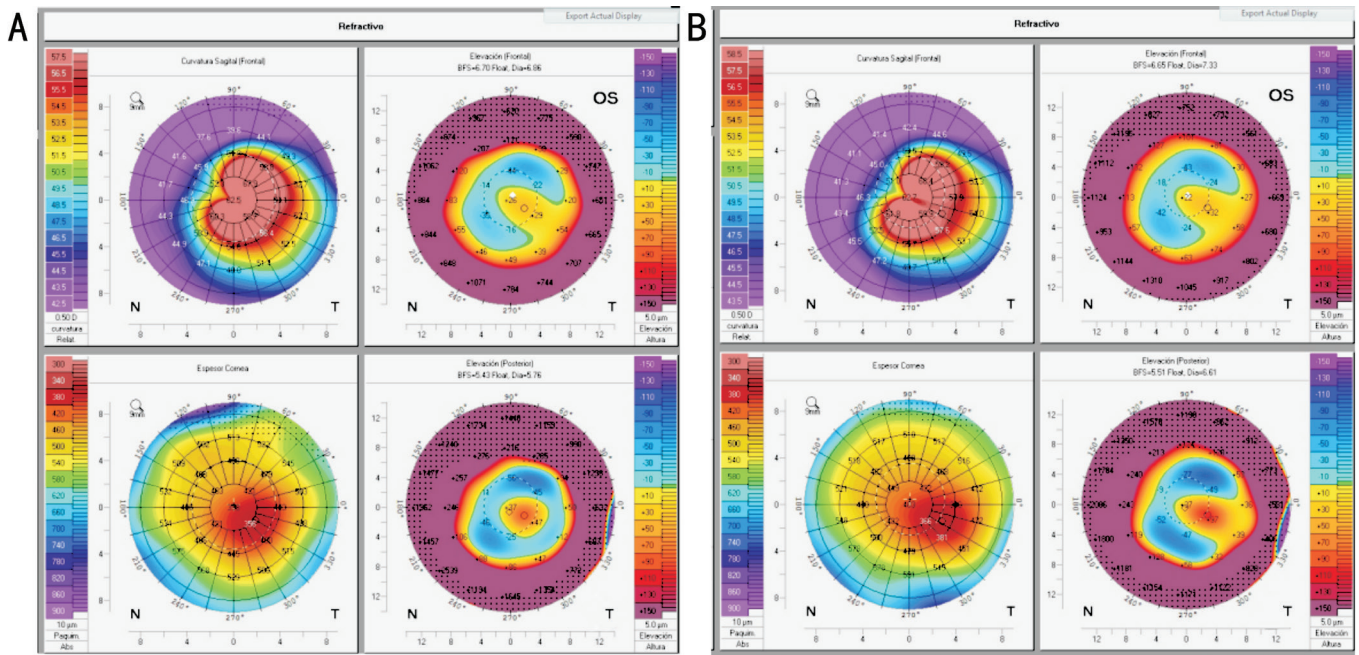


Figure 2 Corneal topography A: LE baseline corneal topography (Oculus, Pentacam): the curvature sagittal frontal map shows an inferior steep with average keratometry (Km) value of 56.2 D, topographic astigmatism of 7.8 D and thinnest pachymetry of 354 μm. A minimum curvature radius (Rmin) of 6.01 mm and abnormal eccentricity (*Q* value of -2.07) classify the disease as level 3 (advanced) keratoconus. B: LE 8mo after transepithelial cross-linking showing similar values [Km 56.5, topographic astigmatism of 9.1 D, *Q* value (asphericity) of -1.4 and thinnest pachymetry of 353 μm] which point to a stabilization of the disease.

and an apparently healthy optic disc with a vertical cup-to-disc ratio of 0.4 in the LE. Both eyes showed arterial vascular tortuosity. The visual field evaluation (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA, USA) showed an increased blind spot in the RE and normal visual field indices for both eyes. The retinal nerve fiber layer thickness as measured by optic coherence tomography (Cirrus OCT, Carl Zeiss Meditec Inc., Oberkochen, Germany) was 97 μm, disc area was 3.66 mm², rim area was 1.13 mm² and vertical cup-to-disc area was 0.78 in the RE. Due to the anterior segment disorder, optic coherence tomography was not reliable for the LE. The axial length was 23.38 mm in the RE and 23.75 mm in the LE.

Sequential corneal topographic studies with Pentacam (Oculus Inc., Germany) confirmed the diagnosis of progressive keratoconus in the LE. Transepithelial cross-linking was performed on the LE, achieving topographic stability with no improvement in the astigmatism. Three years later, two corneal segments (KeraRings) with a thickness of 310 μm (120°/250 μm and 90°/150 μm) were implanted in a concentric intracorneal tunnel created with a femtosecond laser (IntraLase Corp., Irvine, California, USA), which improved the visual acuity and astigmatism in the LE. A year after the last surgery, the uncorrected visual acuity was 20/70 and the best corrected visual acuity was 20/40, with currently stable topography and corneal thickness (Figures 2, 3, 4).

To the best of our knowledge, this is the fourth report of keratoconus associated with WBS and the first case to be

treated with transepithelial cross-linking and corneal segments. This uncommon association of WBS with keratoconus might be explained by the relationship between the risks factors of the two diseases and enables new physiopathological hypotheses to be raised. We hypothesize that a gene is partially responsible for keratoconus might be included in the 7q11.23 deletion, suggesting that the alteration of the elastin gene could lead to the change in corneal viscoelasticity^[4,8]. Understanding the genetic basis of keratoconus essential for developing diagnostic tests, gene therapy and medications in the future. Moreover, keratoconus has been associated with a number of genetic connective tissue disorders (Marfan syndrome, Ehlers-Danlos syndrome and trisomy 21)^[4,7].

Optic disc disorders have been described in 3 of a 16 patients with WBS case series, including two cases of optic disc hypoplasia and one case of increased excavated disc^[2]. To our knowledge, however, this is the first reported case of WBS associated with megalopapilla. Megalopapilla is a developmental anomaly marked by extraordinarily large optic discs (area>2.5 mm² or vertical diameter>2.1 mm), with very large central cups and a narrow but healthy neuroretinal rim. There are two types of megalopapilla: type 1, which is bilateral with a normal configuration, pale surface, high cup-to-disc ratio and a round or horizontal oval cup, and type 2, which is unilateral with a superiorly displaced round cup, with a thinner superior neuroretinal rim and a higher frequency of cilioretinal arteries^[9]. Megalopapilla is easily confused with advanced glaucomatous cupping. Our patient had normal

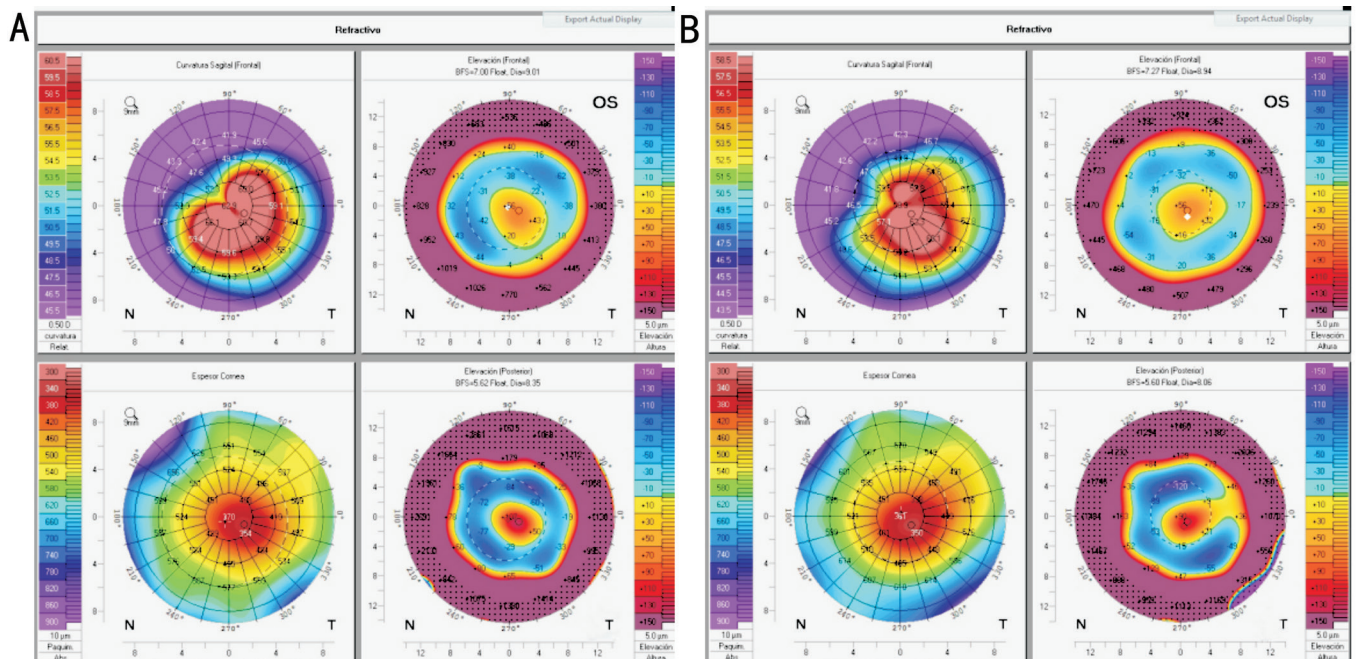


Figure 3 Corneal topography A: LE corneal topography (Oculus, Pentacam) 33mo after transepithelial cross-linking. Astigmatism and thinnest pachymetry are similar to baseline topography 7.6 D and 347 μ m which indicate a stable keratoconus; B: LE corneal topography 4mo after intrastromal corneal ring segment implantation: average keratometry decreased 4.1 D (from 58.5 D preoperatively to 54.4 D postoperatively) and topographic astigmatism decreased 4.5 D (from 7.6 D preoperatively to 3.1 D postoperatively).

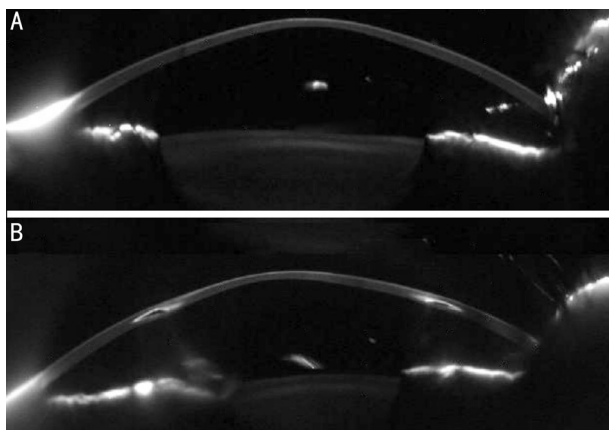


Figure 4 Scheimpflug image A: LE scheimpflug image before corneal segments; B: LE scheimpflug image after corneal segments.

pachymetry-corrected intraocular pressure, and the results of the visual field evaluation and retinal nerve fiber layer by optic coherence tomography were normal. Large eyes with axial myopia have discs that appear larger during direct ophthalmoscopy. In our case, however, the axial length was similar for the two eyes, and the RE even had a lower axial length than the LE. In view of these findings, we believe that our patient presented a megalopapilla in his RE.

We report the first case of megalopapilla associated with WBS. Further studies are warranted to determine whether this is a chance finding or if there is an association between the two pathologies. In light of our patient’s satisfactory outcome, we propose that progressive keratoconus in patients with WBS is treatable with sequential cross-linking and corneal segments.

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Conflicts of Interest: Mediero S, None; D’Anna Mardero O, None; Boto de los Bueis A, None; Noval Martín S, None; García-Miñaur S, None.

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