

Congenital keratoglobus with blue sclera in two siblings with overlapping Marshall/Stickler phenotype

Serhat Imamoglu, Vedat Kaya¹, Ebru Yalin Imamoglu²,
Kemran Gok³

We aimed to describe congenital keratoglobus with blue sclera in two siblings with overlapping Marshall/Stickler phenotype. Two sisters (ages four and six) with bilateral high astigmatism were evaluated by slit-lamp microscopy. Corneal topography and pachymetry maps were also obtained. Slit-lamp examination revealed that both corneas were globular in shape with peripheral corneal thinning. Pachymetry maps showed diffuse corneal thinning. Two siblings had in common the features of keratoglobus, blue sclera, atypical face, hearing loss, and hypermobile joints. We tentatively diagnosed the sisters as having an overlapping Marshall-Stickler phenotype based on clinical and radiological findings. Marshall-Stickler syndrome may exist in the differential diagnosis of keratoglobus with blue sclera.

Key words: Blue sclera, collagen, keratoglobus, Marshall-Stickler

Keratoglobus is a rare noninflammatory corneal thinning disorder characterized by generalized thinning and globular protrusion of the cornea.^[1] The literature contains reports of connective tissue disorders in association with keratoglobus and blue sclera.^[2,3]

Marshall-Stickler syndrome is also a connective tissue disorder characterized by ocular and orofacial abnormalities, arthropathy, and deafness.^[4] Ocular findings include severe myopia, myopic degeneration of the retina, retinal detachment, vitreoretinal degeneration, astigmatism, cataract, strabismus, and glaucoma.^[5] Until now, keratoglobus with blue sclera has not been reported in patients with Marshall-Stickler syndrome. This is the first case report in the literature describing an overlapping Marshall/Stickler phenotype in the differential diagnosis of keratoglobus with blue sclera.

Case Report

In January 2015, two sisters aged four (sibling 1) and six (sibling 2) with asymptomatic, consanguineous (first cousin) parents were referred to our Ophthalmology Department for evaluation of bilateral high astigmatism. Both siblings suffered since birth from poor vision in both eyes and photophobia since birth. Their family history was not remarkable.

On ophthalmological examination, autorefractometer measurements for sibling 1 and sibling 2 were OD $-3.75 - 2 \times 179^\circ$ /OS $-3.75 - 2.75 \times 177^\circ$ and OD $-2.25 - 7.75 \times 166^\circ$ /OS $-3.75 - 5.75 \times 174^\circ$, respectively. Reliable visual acuity measurements could not be obtained in sibling 1, whereas best-corrected visual acuity for sibling 2 was 20/32.

Blue sclera and mild globular protrusion of the cornea were observed bilaterally in both siblings. Slit-lamp examination of the cases revealed that both corneas were globular in shape with peripheral corneal thinning. The remaining anterior segment structures were normal. Intraocular pressures were within normal limits. Fundus and gonioscopic examination of the siblings was also unremarkable.

Corneal topography and pachymetry maps were obtained using a Scheimpflug imaging (Pentacam, Oculus Optikgeräte GmbH, Wetzlar, Germany) [Fig. 1]. Maximal keratometry (K_{max}) indices for sibling 1 and sibling 2 were 52.9 D (OD)/53.5 D (OS) and 54.4 D (OD)/55.4 D (OS), respectively. Pachymetry maps showed diffuse corneal thinning. At the thinnest point, the corneal thickness values for sibling 1 and sibling 2 were 241 μ (OD)/291 μ (OS) and 286 μ (OD)/305 μ (OS), respectively. Ultimately, the diagnosis of keratoglobus was made.

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Department of Ophthalmology, Haydarpaşa Numune Research and Training Hospital, ¹Department of Ophthalmology, Faculty of Medicine, Istanbul Kemerburgaz University, ²Department of Pediatrics, Zeynep Kamil Maternity and Children's Training and Research Hospital, Istanbul, ³Department of Ophthalmology, Mardin Park Private Hospital, Mardin, Turkey

Correspondence to: Dr. Serhat Imamoglu, Haydarpaşa Numune Research and Training Hospital, Tıbbiye Caddesi, No. 40, 34662 Üsküdar, Istanbul, Turkey. E-mail: ophserhat@hotmail.com

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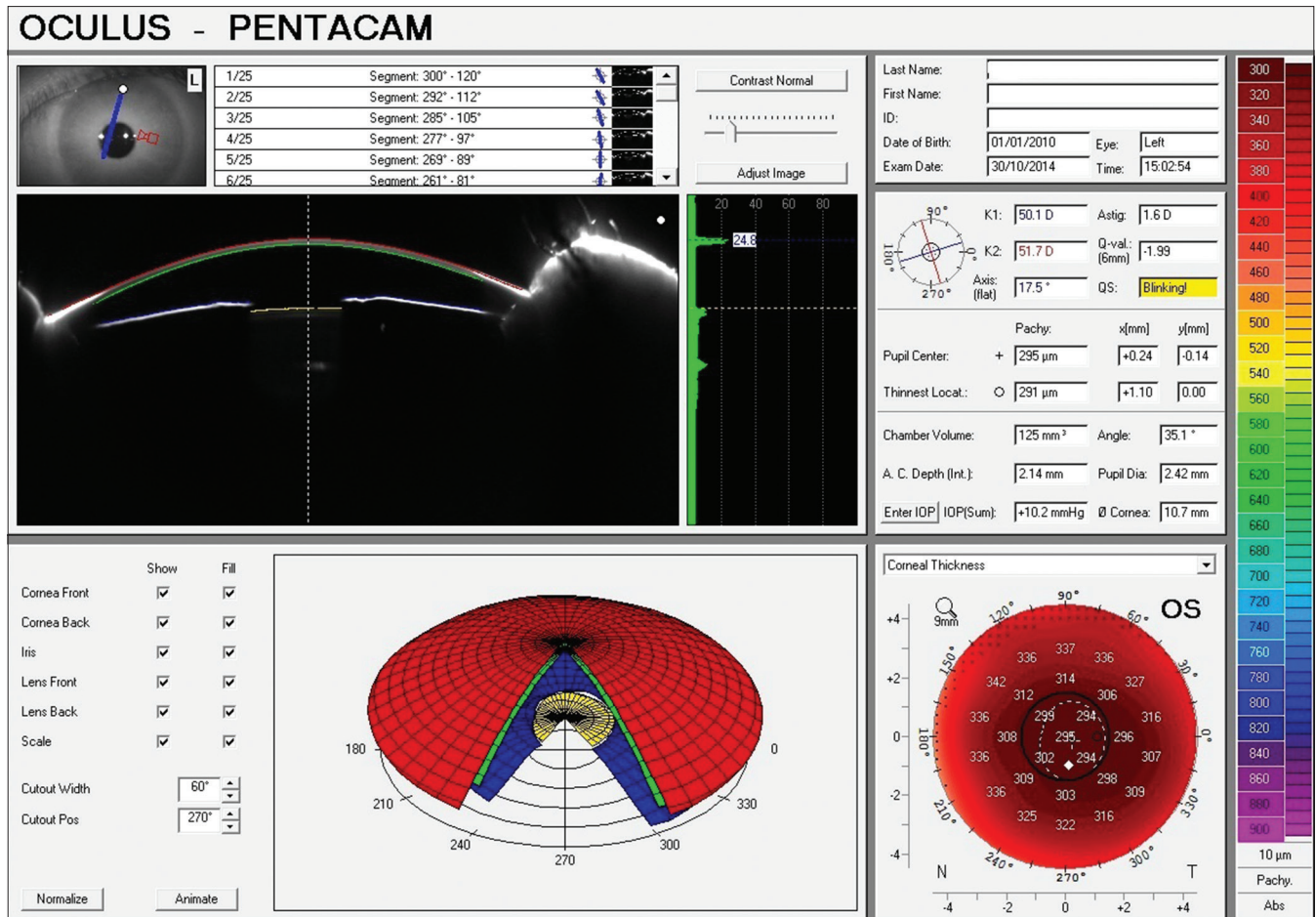


Figure 1: Corneal topographic images of the left eye of sibling 1 showing limbus-to-limbus corneal thinning



Figure 2: Frontal and profile views of sibling 1 (top) and 2 (bottom)

The two siblings had in common the features of keratoglobus, blue sclera, atypical faces, hearing loss, and hypermobile joints [Fig. 2]. Therefore, they were referred to the genetic department for systemic evaluation. On general assessment, the two siblings exhibited normal vital signs. Their height, weight, and head circumference were age appropriate. Both siblings had flat midfaces, large eyes, frontal bossing, mild hypertelorism, calvarial thickening, and absent frontal sinuses, suggesting

a diagnosis of Marshall syndrome [Fig. 3]. These siblings had also mandibular hypoplasia, hyperextensible joints, and metaphyseal widening of long bones, suggesting a diagnosis of Stickler syndrome. Otoacoustic emission test was performed to evaluate hearing loss and was found abnormal in both siblings. Other detailed clinical characteristics of Marshall syndrome, Stickler syndrome, and our cases are presented in Table 1.^[6] We tentatively diagnosed the sisters as having an overlapping Marshall/Stickler phenotype based on clinical and radiological findings. Physical and radiological examination of the parents was unremarkable.

Written informed consent was taken for photography and genetic analysis. We could study only the exon 49 and exon 52 regions of the COL11A1 gene, and the results were negative.

Protective eyeglasses were prescribed for both siblings, and avoidance of contact sports was highly recommended owing to the high risk of perforation.

Discussion

To our knowledge, this is the first report describing congenital keratoglobus with blue sclera in two siblings with overlapping Marshall-Stickler phenotype.

In the past, Marshall and Stickler syndromes were considered to be separate entities. It is proposed that the existing phenotypic overlap suggests that Marshall and

Table 1: Clinical features of Marshall syndrome, Stickler syndrome, and overlapping phenotype of our cases

	Marshall syndrome	Stickler syndrome	Sibling 1 and 2*
Short stature	+	Rare	-
Short nose/flat nasal bridge	+	+	+
Anteverted nares	+	+	+
Flat midface	+	-	+
Appearance of large eyes	+	-	+
Thick lips	+	-	-
Mandibular hypoplasia	-	+	+
Cleft palate	-	+	-
Frontal bossing	+	-	+
Hypertelorism	+	-	Mild
Myopia	+	+	+
Cataract	+	+	-
Esotropia	+	-	-
Glaucoma	Rare	Rare	-
Retinal detachment	Rare	+	-
Vitreous anomaly	-	+	-
Rupture of lens capsule	Rare	-	-
Lens dislocation	-	Rare	-
Hearing loss	+	+	+
Calvarial thickening	+	-	+
Absent frontal sinuses	+	-	+
Falx-tentorial-meningeal calcifications	+	-	-
Brachycephaly	+	-	-
Hypotonia	-	+	-
Hyperextensible joints	-	+	+
Arthropathy	-	+	-
Metaphyseal widening in long bones	-	+	+
Spondyloepiphyseal dysplasia	-	+	-
Mental retardation	Rare	Rare	-

*Both siblings had similar clinical characteristics, so they are presented in one column. +: Seen, -: Not seen



Figure 3: Absence of frontal sinus is seen in X-ray graphy of sibling 2

Stickler syndromes are probably allelic expressions of the same locus.^[7] Therefore, the distinction between the two should be abandoned.

Mutations in the COL11A1 gene resulted in overlapping phenotypes of Marshall and Stickler syndromes.^[8] Although Jun *et al.* demonstrated the expression of the COL11A1 gene in human donor corneas, corneal disease associated with Marshall-Stickler syndrome due to COL11A1 mutation has not yet been reported.^[9]

The altered collagen due to COL11A1 mutation may weaken collagen fibers in the cornea, which could play a role in the development of keratoglobus in these cases. Furthermore, thinning and breakdown of the collagen is the main histological finding in cases of blue sclera.^[3]

In practice, there are difficulties in obtaining whole genome analysis due to size and complexity of the COL11A1 gene and

also to the high cost of these investigations. Only the exon 49 and exon 52 regions of the COL11A1 gene were identified and found to be mutation negative. We could not investigate the remaining exons of the gene. Furthermore, we could not screen the COL2A1 gene in relation to some forms of Stickler syndrome. These were the major limitations of our case presentation.

Khalifa *et al.* pointed out that dominant and recessive mutations in the COL11A1 gene cause Marshall and Stickler syndromes.^[10] In this report, our cases were the offspring of unaffected consanguineous parents, suggesting autosomal recessive inheritance.

Keratoglobus is primarily considered a congenital disorder present since birth.^[2] The congenital form of disorder is always bilateral.^[1] Our cases also showed bilateral involvement.

In the literature, keratoglobus with blue sclera was reported in association with connective tissue disorders. These disorders are Ehlers-Danlos Type VI, Marfan syndrome, Rubinstein-Taybi syndrome, and osteogenesis imperfecta.^[1] Until now, keratoglobus with blue sclera has not been reported in association with Marshall/Stickler phenotype. As a connective tissue disorder, Marshall-Stickler syndrome might be in the differential diagnosis of keratoglobus with blue sclera.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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