Brittle cornea syndrome: A tale of three brothers

Kunal Mandlik, Rakesh A Betdur, Rashmita R, Shivananda Narayana

Brittle cornea syndrome (BCS) is a genetic connective tissue disorder with discernible ocular features such as blue scleral and thin cornea that predominantly presents in younger children. We herein describe cases of three siblings with BCS, two of whom presented to us with open globe injuries following trivial trauma. Clinical examination of the other eye in both showed diffusely thin corneas and blue sclera. A systemic evaluation revealed sensorineural hearing loss and hyperextensible joints. The third sibling was screened and found to have features concurrent with BCS. This report highlights the challenges faced in the management of ocular injuries and consecutive complications in these patients.

Key words: Blue sclera, brittle, thin cornea, trauma

Brittle cornea syndrome (BCS) is a rare genetic condition characterized by the blue sclera, fragile corneas, and progressive myopia along with auditory and musculoskeletal involvement.[1] Recessive mutations in the *ZNF469* and *PRDM5* genes have been implicated in the pathogenesis of this condition,[2] which can frequently be misidentified as connective tissue disorders such as Ehlers–Danlos syndrome, osteogenesis imperfecta, and Stickler syndrome.[3] A timely diagnosis of this condition is crucial and would play a vital role in determining the visual prognosis and quality of life. In this case series, we describe the ocular and systemic findings in three siblings with BCS, born to a non-consanguineous Indian couple.

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Cornea and Refractive Services, Aravind Eye Hospital, Puducherry, India

Correspondence to: Dr. Rashmita R, DNB, Fellow, Cornea and Refractive Surgery, Aravind Eye Hospital, Puducherry - 605 007, India. E-mail: rashmita2992@gmail.com

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Case Reports

Case 1

A 4-year-old boy presented to us following a trivial injury to the left eye with a toy. Examination showed a large full-thickness corneal tear, with vitreous and lens matter in the anterior chamber [Fig. 1a]. Binocular visual acuity was 6/9.5 on Cardiff Acuity Test. Visual acuity in OS was light perception. The other eye showed blue sclera and a diffusely thin cornea. A clinical diagnosis of BCS was made, and he was taken up for a corneal tear repair with lens aspiration. The surgery posed challenges such as cheese-wiring of the cornea and extension of the side port [Table 1]. Postoperatively, the anterior chamber was formed, and the wound subsequently healed with a central scar and peripheral anterior synechiae [Fig. 1b]. B-scan done in the immediate postoperative period showed an anechoic vitreous cavity. His systemic evaluation revealed hyperextensible joints and hearing defects on Brainstem Evoked Response Audiometry (BERA). Suture removal done 2 months after the primary repair led to gaping of the wound due to poor wound integrity despite scarring and had to be re-sutured. His two elder brothers were called in for an evaluation and were also found to have BCS. The parents were informed about the risks of open globe injuries in the future and advised protective measures to avoid ocular trauma. Nine months later,

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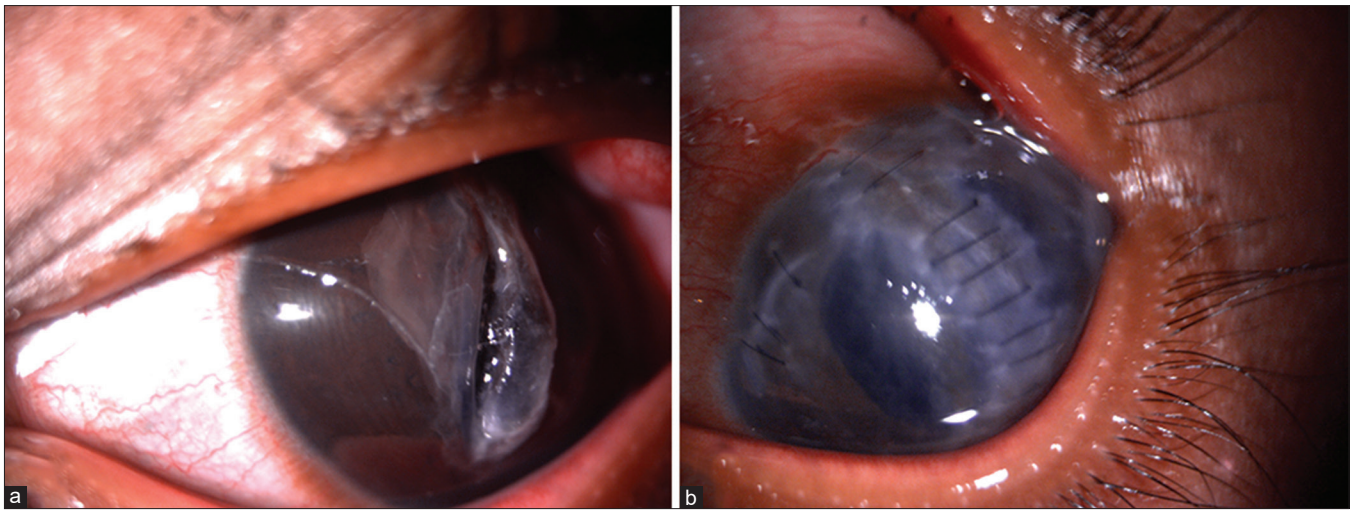

Figure 1: (a) Diffuse slit-lamp image of the eye showing a large vertical full-thickness corneal tear. (b) Postoperative diffuse slit-lamp image showing a sutured corneal tear

Table 1: List of intraoperative complications faced while operating on cases with brittle cornea syndrome

Intraoperative challenges faced	How to prevent/manage
Cheese-wiring of the cornea while suturing	Take long suture bites, avoid overtight sutures
Difficulty in burying corneal sutures	Sutures may have to be left unburied to avoid cheese-wiring, a BCL can be applied to avoid postoperative irritation
Extension of corneal side port and sclerotomy ports	Minimal manipulation through the ports. Avoid applying stress over the wound margins and suture the ports at the end of the surgery
Leaky corneal wound	Cyanoacrylate glue with BCL can be placed
Construction of a sclerocorneal tunnel	Meticulous tunnel construction to prevent buttonhole and premature entry, avoid dissecting a deeper plane

BCL: bandage contact lens

he suffered another minor injury to the operated eye while playing with his elder brother, who also sustained an ocular injury. Examination showed hyphema, which was managed medically and resolved in due course.

Case 2

The elder sibling, a 7-year-old, presented to us following minor ocular trauma. His examination showed diffuse corneal thinning with blue sclera in both eyes [Fig. 2b], and a large full-thickness corneal laceration extending from the superior to inferior limbus through the central cornea along with iris prolapse OD. His best-corrected visual acuity (BCVA) was 6/36 OD and 6/9 OS. Corneal topography done before evaluation showed diffuse corneal thinning with a central corneal thickness (CCT) of 282 µ OD and 304 µ OS. The corneal tear repair presented similar challenges such as the previous case. The wound healed with a central scar, as seen 2 months after the primary repair. Four months later, he developed a visually significant cataract OD, and a lens aspiration through a temporal sclerocorneal tunnel was planned. The tunnel was meticulously constructed to prevent any complications due to the fragile sclera and cornea. There was an extension of the corneal side port due to the brittle cornea and it was secured with a 10–0 Nylon suture along with cyanoacrylate glue and a bandage contact lens. This is the first reported case of lens aspiration through a sclerocorneal tunnel in a patient with BCS to the best of our knowledge. His immediate postoperative B-scan was within normal limits. His BCVA was 6/60 OD and 6/9 OS. Akin to his brother, he exhibited hyperextensible joints [Fig. 2c] and sensorineural hearing loss on BERA.

Case 3

The eldest sibling, an 11-year-old, had blue sclera and diffuse corneal thinning bilaterally. His retinoscopy was –4D Cyl × 180^0 OD and –7D Sph –4D Cyl × 15^0 OS. His BCVA was 6/9 OD and 6/18 OS. Fundus examination OU was within normal limits. The systemic evaluation did not reveal any abnormalities. Corneal topography showed a CCT of 243 µ OD and 253 µ OS [Fig. 2a]. He was advised to avoid contact sports and adopt protective lifestyle changes. The significance of regular eye check-ups was clearly explained to the parents.

The parents had a non-consanguineous marriage. The father was deaf and mute since childhood, but no other systemic or ocular defects were noted. The mother's ocular and systemic evaluation did not show anything remarkable. The genetic analysis would have been desirable in these patients but was not done due to the parents' financial constraints.

Discussion

Brittle cornea syndrome is a connective tissue disorder with predominantly ocular involvement and understated systemic features such as developmental dysplasia of the hip, hypermobility of small joints, and sensorineural hearing loss. It is often confused with the likes of Ehlers–Danlos syndrome or osteogenesis imperfecta, which have more obvious systemic signs from early life.[3] Although uncommon, ocular rupture is a feature of Ehlers–Danlos type VI (EDS VI), and it is the

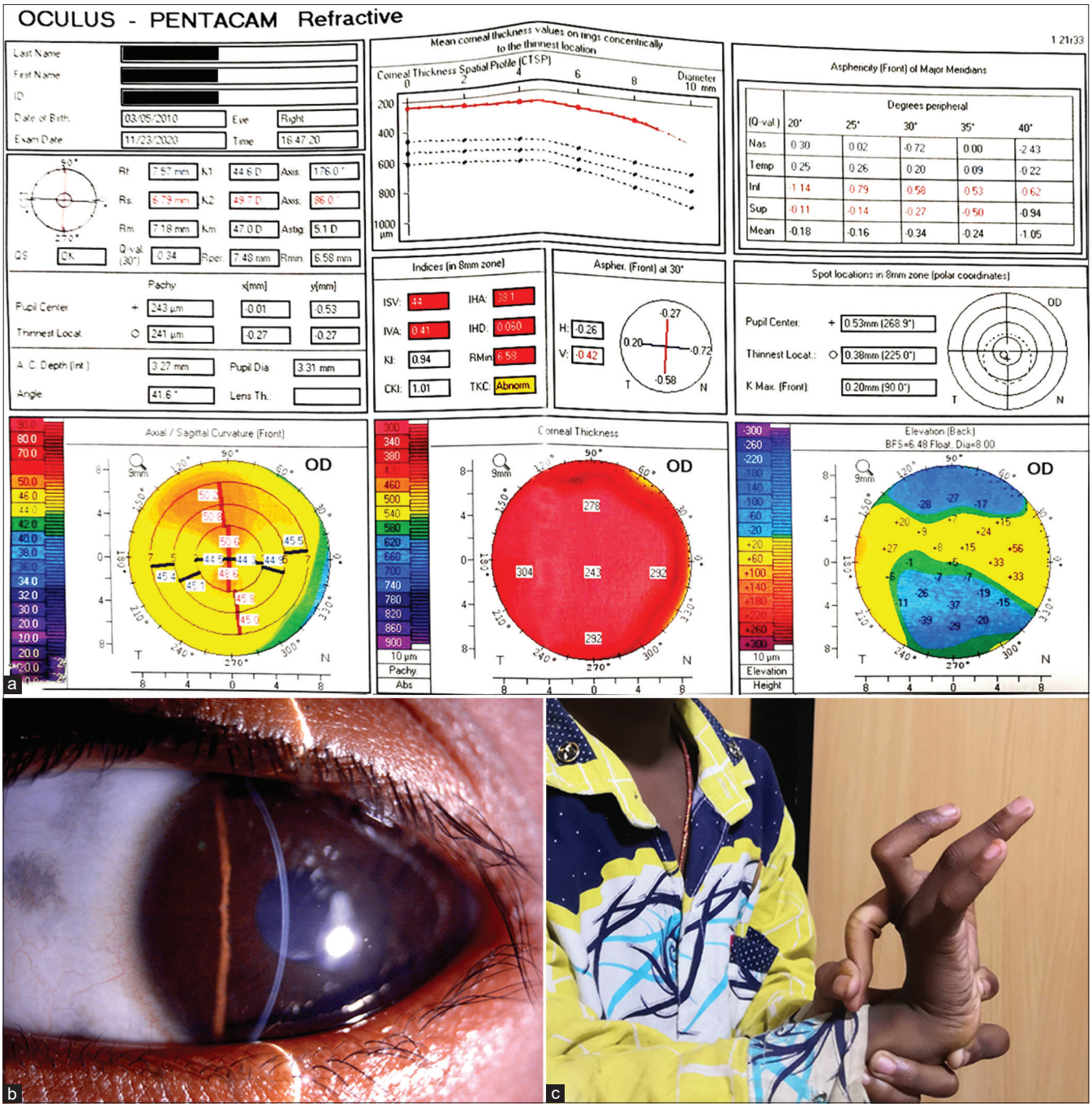

Figure 2: (a) Topography showing diffusely thin cornea on pachymetry map and abnormal keratometry values. (b) Slit-section showing thin cornea and adjacent blue sclera. (c). Hyperextensible metacarpophalangeal joint

sclera that is more susceptible to rupture. Features such as severe muscular hypotonia at birth, progressive kyphoscoliosis in early infancy, the fragility of skin with abnormal scarring, severe joint hypermobility and luxations, Marfanoid habitus, osteopenia, and cardiopulmonary insufficiency are characteristic of EDS VI and have not been reported in cases of BCS. Corneal topography in BCS shows a diffusely thin cornea with a CCT less than 400 μ and has been reported to be less than 300 μ in some cases. However, features of keratoconus or keratoglobus such as posterior elevation and stromal striae are notably absent.[3] Corneal thinning is also seen in other connective tissue disorders; however, the thinning is not as profound. Confirmatory diagnosis and definitive differentiation from other connective tissue disorders can be made by genetic analysis to look for mutations in the *ZNF469* gene (Type 1) and *PRDM5* gene (Type 2).[4] *ZNF469* gene has been found to be associated with CCT and anterior segment development while the *PRDM5* gene is responsible for extracellular matrix physiology.[3,5]

BCS is a vastly underdiagnosed entity and goes unnoticed until the patient is exposed to ocular trauma or even spontaneous rupture, after which the visual outcome is

inexorably poor. Penetrating keratoplasty (PK) would be excessively challenging owing to the fragility of the cornea and sclera, large grafts, and difficulty in suturing.[6] Complications such as secondary glaucoma can occur post PK or repair of an open globe injury, further deteriorating the visual prognosis. Lifestyle measures to protect the eyes from injury are of paramount importance. Polycarbonate glasses can effectively protect the eyes from trivial injuries. Although systemic complications such as arterial rupture and death due to cardiopulmonary insufficiency have not yet been reported in patients with BCS, caution must be exercised, and these patients should undergo periodic systemic assessments.

Conclusion

In this case series, two of the three siblings suffered an open globe injury following minor trauma to the eye. The visual outcome was poor owing to large scars, irregular astigmatism, and aphakia. Another potential complication to watch out for is the development of secondary glaucoma and cataract. This report describes the consequences of trivial ocular injuries in patients with BCS and reiterates the need for lifestyle changes and protective measures to preserve and sustain the existing vision and quality of life.

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Conflicts of interest

There are no conflicts of interest.

References

1. Ramappa M, Wilson ME, Rogers RC, Trivedi RH. Brittle cornea syndrome: A case report and comparison with Ehlers Danlos syndrome. J AAPOS 2014;18:509-11.
2. Abu A, Frydman M, Marek D, Pras E, Nir U, Reznik-Wolf H, *et al*. Deleterious mutations in the zinc-finger 469 gene cause brittle cornea syndrome. Am J Hum Genet 2008;82:1217-22.
3. Walkden A, Burkitt-Wright E, Au L. Brittle cornea syndrome: Current perspectives. Clin Ophthalmol Auckl NZ 2019;13:1511-6.
4. Wan Q, Tang J, Han Y, Xiao Q, Deng Y. Brittle cornea syndrome: A case report and review of the literature. BMC Ophthalmol 2018;18:1-5. doi: 10.1186/s12886-018-0903-2.
5. Vincent AL, Jordan CA, Cadzow MJ, Merriman TR, McGhee CN. Mutations in the zinc finger protein gene, ZNF469, contribute to the pathogenesis of keratoconus. Invest Ophthalmol Vis Sci 2014;55:5629-35.
6. Eleiwa T, Raheem M, Patel NA, Berrocal AM, Grajewski A, Abou Shousha M. Case series of brittle cornea syndrome. Case Rep Ophthalmol Med 2020;2020:4381273. doi: 10.1155/2020/4381273.