Cornea 18(5): 621–624, 1999.

Bilateral Spontaneous Corneal Rupture in Brittle Cornea Syndrome: A Case Report

Luis Izquierdo, Jr., M.D., Mark J. Mannis, M.D., Peter B. Marsh, M.D., Samuel P. Yang, M.D., and J. Martin McCarthy, M.D.

Ehlers–Danlos syndrome (EDS) is a heterogeneous group of connective tissue disorders, characterized by hyperextensibility of the joints and skin, easy bruisability, and the formation of characteristic "cigarette paper" scars (1). At least 10 clinical variants of EDS have been identified (2). Of particular interest to the ophthalmologist is EDS type VI, the ocular–scoliotic variant, accounting for 2% of EDS cases. EDS type VI is biochemically characterized by deficient activity of the enzyme lysyl hydroxylase, which produces defective cross-linking of collagen. Clinically important features of EDS type VI include ocular and arterial fragility, scoliosis, and hyperextensibility of the joints (3). There exists another syndrome in which the clinical findings are similar, including spontaneous rupture of the globe, sometimes referred to as the brittle cornea syndrome (BCS), fragilitis oculi, or blue sclerae with keratoglobus/keratoconus. However, in this autosomal recessive condition, there is no lysyl hydroxylase deficiency. In this report, we present a patient with BCS and spontaneous bilateral corneal perforation requiring a penetrating keratoplasty in the right eye.

CASE REPORT

A 5-year-old Pakistani boy complaining of decreased vision and tearing in his right eye was admitted to the Cornea Service at the University of California, Davis, in May 1998. His ocular history was significant for a corneal rupture in the left eye in September 1996, noted 3 days after a minor injury to the forehead. The same cornea ruptured spontaneously again in August 1997. Although repair of the corneal ruptures was accomplished, there was loss of light perception, and a total retinal detachment was seen on ultrasound. In September 1997, a spontaneous corneal rupture of his right eye occurred and was repaired primarily in Pakistan. Family history revealed significant consanguinity. The child's parents were first cousins. The parents also have two first cousins with an identical ocular history who are now completely blind. These siblings were also the product of a marriage between first cousins.

Physical examination revealed normal head circumference and black hair, along with mild hyperextensibility of all joints except for the left elbow (Fig. 1). The skin was notable for characteristic depressed "cigarette paper" scars over the forehead and shins. The spine and chest were normal without clinical evidence for mitral valve prolapse. Visual acuity was counting-fingers at 2 feet in the right eye and no light perception in the left eye.

The child was examined under anesthesia. Examination revealed blue sclerae, bilateral corneal scars, and an enlarged corneal diameter (13.5 mm OU). In the left cornea, there was a central leukoma with adherent iris. The anterior chamber was flat superiorly and formed but very shallow inferiorly. Examination of the right eye revealed a nasal rupture site, which had been sutured. The anterior chamber was shallow but formed, and there was a central corneal scar, which extended to the previous rupture site nasally (Fig. 2). Intraocular pressures measured with a Tonopen were 8 mm Hg in the right eye and unmeasureable in the left eye. The A/B scan demonstrated a total retinal detachment in the left eye.

A skin-punch biopsy was taken for fibroblast culture studies, and urine was obtained for analysis of pyridinium cross-links. Subsequent laboratory results indicated normal urinary excretion of pyridinium cross-links (4) and the presence of lysyl hydroxylase activity in cultured fibroblasts at 63% of control values, suggesting that this case did not represent EDS type VI.

Submitted August 29, 1998. Revision received December 22, 1998. Accepted February 14, 1999.

From the Cornea and External Disease Service, Department of Ophthalmology, and the Genetic Service Department of Pediatrics, University of California, Davis, Sacramento, California, U.S.A.

Address correspondence and reprint requests to Dr. M.J. Mannis, 4806 Y Street, Suite 2400, Sacramento, CA 95817, U.S.A. E-mail: mjmannis@ucdavis.edu

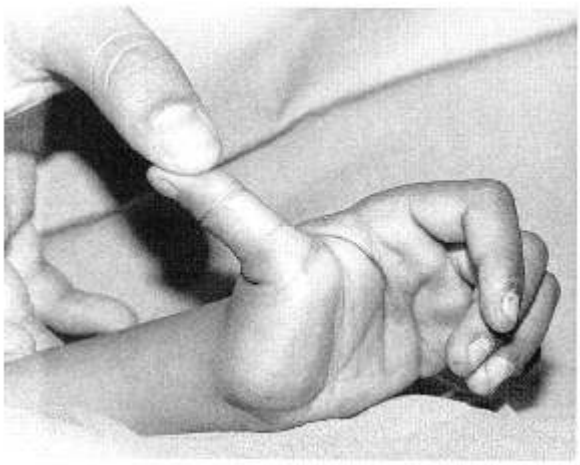

FIG. 1. Hyperextensibility of joints.

Audiologic evaluation was performed because of speech delay and middle ear effusions. Besides the expected conductive hearing loss at low frequencies, a moderate sensorineural hearing loss (35–55 dB) was found at higher frequencies (4,000–8,000 Hz).

At a subsequent date, a penetrating keratoplasty was performed on the right eye. A 9.0-mm trephine was used to demarcate the area of the cornea to be removed. A similar-sized trephine was used for the donor cornea. There were multiple iridocorneal synechiae, which required lysis by using a Vannas scissors and a Barraquer sweep. The crystalline lens appeared to be clear. The donor cornea was sutured with 10-0 monofilament nylon with sutures placed in a radial interrupted fashion. Care was taken to place the sutures deeply in the donor tissue and full-thickness in the recipient. The surgeon also attempted to make the sutures as long as possible on the recipient side to maximize closure without focal stress on the marginal tissue. At the 6 o'clock position, there was a spontaneous corneal rupture during the rotation of the suture to bury the knot. This required the placement of a small corneoscleral patch, which was covered with a bandage contact lens. The excised cornea was characteristically thinned (Fig. 3).

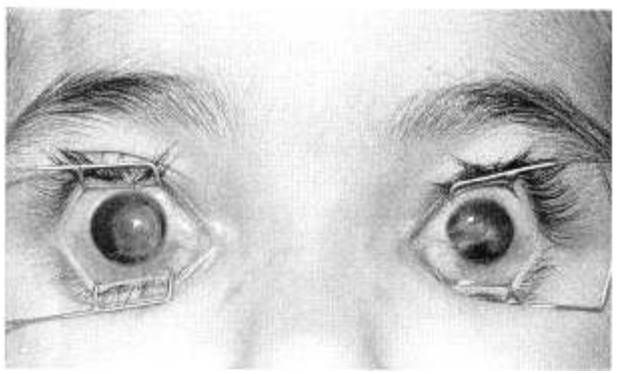

FIG. 2. Corneal scars after bilateral spontaneous corneal rupture and repair.

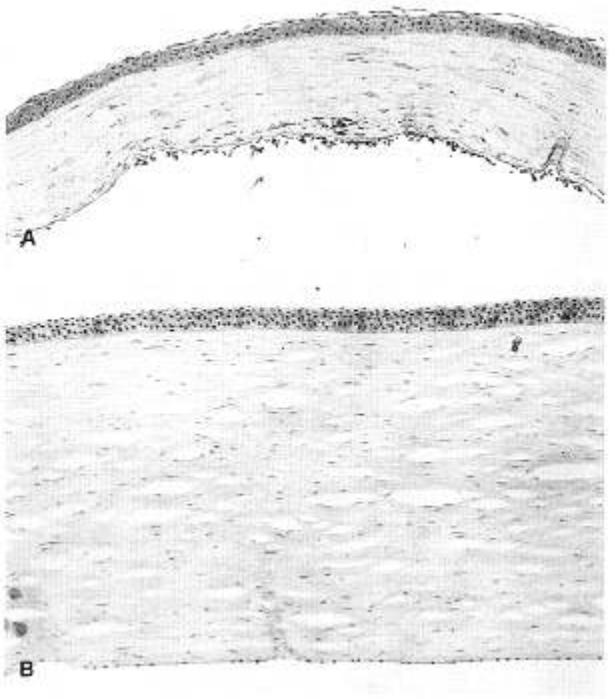

FIG. 3. A: Histopathologic specimen from the patient with brittle cornea syndrome. **B:** Normal corneal histopathology for thickness comparison.

At a subsequent examination under anesthesia, ~2 weeks after the surgery, the graft appeared to be clear and well apposed, and the wound was Seidel negative. Examination of the fundus revealed a normal disc, vessels, and macula. Visual acuity improved to 20/100, and visual function improved over the weeks after surgery.

DISCUSSION

Beighton (5) first recognized a distinct ocular form of EDS in 1970. This autosomal-recessive form of EDS became known as type VI. In type VI, the collagen is deficient in hydroxylysine, which is necessary for the synthesis of stable collagen cross-links. At least two subtypes of EDS type VI are known to exist, based on the hydroxylysine content in skin and the level of lysyl hydroxylase activity present in fibroblasts (6). The first subtype, EDS VI-A, is associated with the absence of hydroxylysine in skin collagen and low levels of lysyl hydroxylase activity in cultured skin fibroblasts. It is characterized by severe dermal, skeletal, and ocular abnormalities. The second subtype, EDS VI-B, also has low levels of lysyl hydroxylase activity but nearly normal levels of hydroxylysine in skin collagen. Its clinical picture is similar to that of EDS VI-A. A third subtype, referred to by some as EDS VI-C, has normal amounts of hydroxylysine in skin collagen and normal levels of lysyl

hydroxylase activity. Patients with this condition have predominantly ocular rather than vascular, dermal, or skeletal findings. A better term would be the BCS (7) because the basic defect does not involve the enzyme lysyl hydroxylase.

Our patient has BCS rather than EDS type VI, based on the results of urinary and enzymatic studies (Table 1). The lysyl hydroxylase activity is in the heterozygote range, so further molecular and biochemical analyses are being pursued. We did not measure skin hydroxylysine content of skin collagen because of the large specimen size required and concern about complications such as abnormal scarring.

Blue sclerae are described in both EDS type VI and BCS, but sensorineural hearing loss has been reported only in BCS (8). Because almost all the cases of BCS have occurred in consanguineous families, some of the associated features, such as red hair and perhaps sensorineural hearing loss, could be due to other recessive genes that are syntenic to BCS (9).

The differential diagnosis includes osteogenesis imperfecta, in which the three primary signs are blue sclerae, deafness, and bone fractures (10,11). Because osteogenesis imperfecta is a disease of type I collagen, it is not surprising that some patients may have skin and joint manifestations that are similar to those found in EDS.

The risk for recurrence of autosomal recessive conditions is 1:4 (25%) for each child. Prenatal diagnosis is possible for EDS type VI (12) but not for BCS. Pregnancy may be hazardous for patients with EDS type VI because of risk for arterial rupture. The prognosis is generally better in BCS than in EDS type VI, because problems are localized to the eyes. However, specific treatment with high-dose ascorbate has been show to help EDS type VI patients, both clinically and in fibroblast culture studies (13).

Prevention of ocular trauma both before and after surgery in patients with known ocular fragility in this and other conditions may avoid corneal rupture. The use of life-long protective eyewear in these patients has been rightly advocated (14).

The surgical management of patients with corneal rupture in EDS type VI is technically challenging and fraught with difficulty. Macsai et al. (15) reported a technique in which they preceded an optical penetrating keratoplasty with a tectonic full-thickness corneal–scleral onlay. The onlay graft served as an anatomically stable substrate into which they were able to perform a successful penetrating keratoplasty subsequently. Variations of this reinforcement technique have been used in other thinning conditions. Full-thickness and lamellar patch grafts (16), "face-lift techniques," and wedge resections (17) have been used in disorders in which the thinning is focal or limited in extent, such as infectious ulceration, pellucid marginal degeneration, and Terrien's degeneration. Surgical options in the presence of diffusely thinned recipient tissues are limited. The most common approach is taking longer bites into the recipient cornea to produce a secure graft–host interface and to minimize the risk of "cheese-wiring" of the suture. Scleral or corneal allografts used to patch weak areas may also be helpful. To avoid suture tract leaks, the judicious use of 11-0 nylon may be employed, although we did not use this technique. In the present case, we performed a penetrating graft without first placing an epigraft of the type described by Macsai et al. (15) or by Cameron et al. (18) in a case of BCS. We elected a more traditional approach to expedite the child's visual rehabilitation and subsequent return to his homeland. Nonetheless, the procedure was complicated by an intraoperative corneal rupture simply from the attempted rotation of nylon knot. A scleral patch graft was used to seal this area. Obtaining a watertight closure without producing a corneal rupture was difficult because of the disparity in donor and recipient tissue thickness combined with the fragility of the recipient bed. A secure wound was finally obtained with 15 sutures and a scleral patch graft from the donor rim at the site that ruptured during knot rotation. Recurrent thinning of the donor cornea did not occur in this patient and

TABLE 1. *Comparison of brittle cornea syndrome and Ehlers–Danlos type VI*

	Brittle cornea syndrome	Ehlers–Danlos type VI
Enzyme abnormality (6)	None	Deficient lysyl hydroxylase activity
Collagen hydroxylysine (6)	Normal	Low
Urinary pyridinium cross-links (4)	Normal	Low
Inheritance	Autosomal recessive	Autosomal recessive
Eye findings (3)	Ocular fragility	Ocular fragility
	Spontaneous rupture	Spontaneous rupture
	Blue sclera	Blue sclera
	Keratoconus	Myopia
	Keratoglobus	Retinal detachment
Hearing abnormalities (8)	Sensorineural hearing loss	None
Systemic findings (1,3,7)	Predominantly ocular	Arterial fragility
		Mitral valve prolapse
		Kyphoscoliosis
		Joint hyperextensibility

has not previously been recognized. However, few cases of BCS have been reported.

This case illustrates the characteristic findings and clinical course in BCS as well as the importance of using specific diagnostic techniques used by clinical and laboratory geneticists, and underscores the challenges in the surgical management of this difficult disorder.

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