Orbscan mapping in Ehlers-Danlos syndrome

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A candidate for refractive surgery presented with classic (type I) Ehlers-Danlos syndrome (EDS). Clinical examination revealed blue sclera, limbus-to-limbus corneal thinning, myopia, and astigmatism. Orbscan® (Bausch & Lomb) pachymetry mapping provided a striking demonstration of the limbus-to-limbus thinning with a central corneal thickness of 360 μm in the right eye and 383 μm in the left eye and midperipheral corneal thickness ranging from 370 to 438 μm and 376 to 434 μm, respectively. Despite the theoretical biomechanical weakness from the thin cornea and defective collagen, regular surface topography was maintained without the development of keratoconus. Although all types of EDS remain a contraindication to laser refractive surgery, Orbscan mapping provides a valuable insight into corneal shape and thickness in this condition.

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All types of Ehlers-Danlos syndrome (EDS) are widely accepted as contraindications to laser refractive surgery. Earlier numerical classifications of EDS were recently changed to 6 distinct clinical types through the addition of molecular and biochemical diagnostic criteria.[1] In this paper, I have adopted the new classification but retained the old classification in parentheses: classic (I, II), hypermobility (III), vascular (IVa, IVb, IVc), kyphoscoliosis (VI, VIa, VIb), arthrochalasis (VIIa, VIIb), and dematosparaxis (VIIc). Former EDS types V (2 families reported), VIII (a few families reported), and X (1 family reported) have been moved to an "others" category, and type IX is no longer considered an EDS phenotype.[1]

Although the molecular basis of EDS is heterogeneous, 3 fundamental mechanisms of disease are known to produce EDS: a deficiency of collagen-processing enzymes, dominant negative effects of mutant collagen α-chains, and haploinsufficiency. These compromise the strength of the connective tissue complex, often the collagen fibril itself. It is the abnormal collagen strength that contraindicates laser refractive surgery as the risk for postoperative ectasia is presumed to be higher and a serious intraoperative complication such as globe rupture is possible.

We report the clinical findings in a patient with classic EDS (I) who presented for laser refractive surgery.

Case Report

A 54-year-old woman presented for laser in situ keratomileusis (LASIK). She had tried contact lenses but had not been successfully fitted, citing discomfort with hard and soft contact lenses. The patient wanted to be spectacle free for thespian activities. She volunteered the diagnosis of EDS type I, which she believed did not affect her eyes. The patient's health was otherwise unremarkable, and hormone replacement therapy was the only medication.

She had worn glasses for myopia since the age of 10 but said the prescription had been stable for many years. She currently wore varifocals with $-3.00\ -1.50 \times 158$ in the right eye and $-5.50\ -1.00 \times 28$ with a +2.00 diopter (D) add in both eyes. No improvement was found with manifest refraction. The best corrected visual acuity was 6/4.8 and N4 in the right and left eyes.

The scotopic pupil size was 4.50 mm in both eyes, and the intraocular pressure was 14 mm Hg. Slitlamp examination revealed blue sclera, clear but thin corneas, and otherwise normal anterior and posterior (no angioid streaks) segments. Retinoscopy reflexes were regular, and no findings suggestive of keratoconus were noted. Orbscan® II (Bausch & Lomb)

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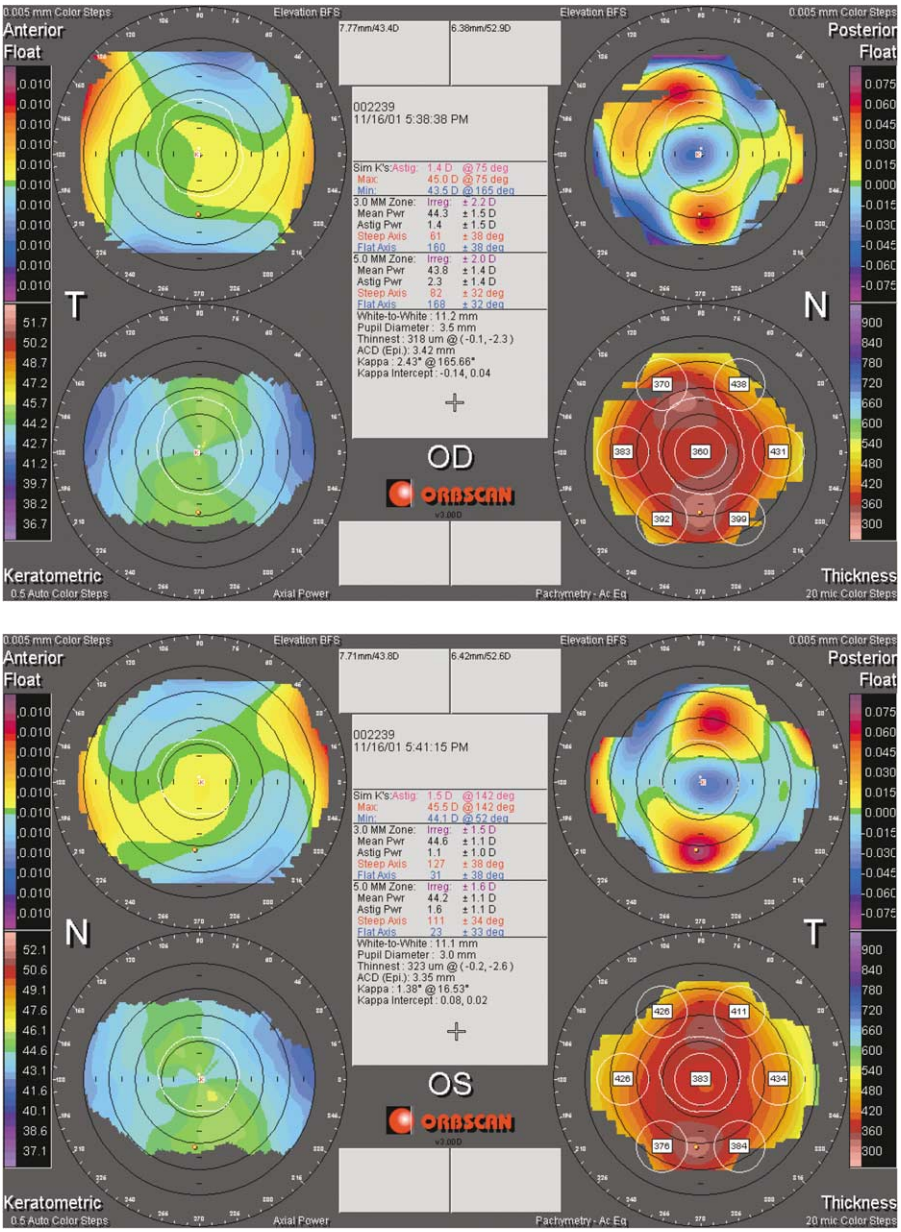

Figure 1. (Pesudovs) *Top:* Orbscan map of the right eye. *Bottom:* Orbscan map of the left eye.

topography demonstrated a normal anterior float and regular topography with 1.50 D with-the-rule astigmatism in each eye (Figure 1). The corneal curvatures were within normal limits with simulated keratometry of 43.5 × 45.0 in the right eye and 44.1 × 45.1 in the left eye. However, the pachymetry maps were striking, with a central corneal thickness of 360 μm in the right eye and 383 μm in the left eye and a midperipheral corneal thickness ranging from 370 to 438 μm and 376 to 434 μm, respectively.

Ultrasound pachymetry confirmed the corneas were unusually thin, although the measurements were significantly greater than Orbscan measurements, with a central corneal thickness of 440 μm in the right eye and 439 μm in the left eye. The acoustic adjustment factor for the Orbscan was set at 0.92, although this explained only half the discrepancy between the 2 measurements. Orbscan minimum corneal thickness measurements were 318 μm in the right eye and 323 μm in the left eye, which corresponded to points of maximum posterior elevation of 2.3 mm in the right eye and 2.6 mm in the left eye below the corneal center. Posterior elevations were unusually high, with maximum elevations of approximately 65 μm and 80 μm, respectively. The patient was denied LASIK.

Discussion

The cardinal features of EDS are hyperextensible skin, hypermobile joints, easy bruising, and fragility of connective tissues, leading to a variety of clinical

manifestations. These features vary depending on the type of EDS. The demonstration of cutaneous hyperextensibility as opposed to lax or redundant skin is tantamount to a diagnosis of EDS, but the skin could still have minimal elasticity. Possibly more than half of all patients with unequivocal signs cannot be fit easily into the classification system,[2] and as more biochemical studies are completed, it is likely that the classifications will change.

Classic EDS (I, II) is characterized by skin hyperextensibility and joint hypermobility, atrophic scars, easy bruising, and autosomal dominant inheritance. Although missense and splice site mutations in both type V collagen genes cause classic EDS (I, II) phenotype (25% to 45% of individuals), other mutations may play a role, including in the tenascin X gene.[3] Hypermobility EDS (III) is characterized by joint hypermobility, pain, dislocations, lack of skin scarring, and autosomal dominant inheritance, but the gene defect is unknown. Vascular EDS (IV) is characterized by thin and translucent skin with highly visible veins, arterial, bowel or uterine rupture, bruising but minimal joint hyperextensibility, and autosomal dominant inheritance. A number of causative mutations in the type III collagen gene have been reported.[4]

Kyphoscoliosis EDS (VI) is characterized by hypotonia, joint laxity, hyperextensible skin, congenital scoliosis, ocular fragility, and autosomal recessive inheritance. Five mutations of the PLOD1 (lysyl hydroxylase 1) gene have been described.[4,5] Arthrochalasia EDS (VIIa, VIIb) is characterized by severe joint hypermobility, congenital hip dislocation, mild skin hyperextensibility, scoliosis, bruising, and autosomal dominant inheritance. This is usually from the loss of the substrate sequence for the N-terminal procollagen protease in 1 of the chains of type I procollagen.[4]

Dermatosparaxsis EDS (VIIc) is characterized by severe skin fragility, cutis laxa, easy bruising, marked joint hypermobility, blue sclera, small jaw, hypertrichosis, and autosomal recessive inheritance. The molecular flaw is type I collagen N-terminase deficiency.[4]

Although vascular EDS (IV) affects type III collagen, which is abundant in blood vessels, the skin is dramatically affected, appearing thin and translucent despite minimal type III collagen in normal skin. In the cornea, collagen type I predominates (~70% of dry weight) and types V, VI, and possibly III are also present,[6] but the existence of corneal thinning and keratoconus[7] in vascular EDS also illustrates the complexity of collagen physiology in the cornea and that ocular complications are possible in all types of EDS.

In a survey of 100 EDS cases, the most frequent ophthalmic findings were epicanthic folds (27%); myopia (8%); blue sclera (7%); strabismus (7%); and frequent floppy upper eyelids, redundant skin on the upper eyelids, and widely spaced eyes.[8] Also reported were limbus-to-limbus corneal thinning,[9] lens subluxation,[10] angioid streaks,[11] retinal detachment (RD),[12] and macular degeneration.[13] Corneal findings include keratoconus,[14] keratoglobus,[15] cornea plana,[9,16] posterior keratoconus,[16] corneal opacity,[16] and microcornea.[9,16] Acute hydrops has been reported in patients with EDS and keratoconus or keratoglobus, but not without either.[9] Ocular fragility, in which the corneal ruptures with minimal trauma[10,12,15] was reported in 7 of 11 cases in 1 series.[9] However, this only occurs in kyphoscoliosis (VI) EDS. This type is uncommon, with only 50 or so cases reported.[17–19] It was previously called ocular–scoliotic type (type VI) because it was characterized by ocular findings disproportionate to systemic findings; however, ocular complications are not always present.

Keratoconus, blue sclera, lens subluxation, or RD are particularly severe in the kyphoscoliosis (VI) type but may occur in all types.[4,5] A recent study of corneal topography in 72 eyes of 36 EDS cases with classic, hypermobile, vascular, and kyphoscoliosis types (I, II, III, IV, and VI) found no cases with slitlamp or retinoscopy findings suggestive of keratoconus.[20] Only 1 case had asphericity and profile difference maps suggestive of mild keratoconus, but no case had interior–superior values greater than the 1.60 threshold.[21]

The apparent rarity of keratoconus in EDS despite collagen deficiencies likely to cause weak corneas and, if our case is typical, thin corneas, is interesting. That regular corneal topography is maintained despite the risk factors for keratoconus suggests a cofactor or precipitating event is required to trigger ectasia is these eyes. Although keratoconus may be rare in EDS, 1 series of 44 keratoconus cases reported 22 cases with joint hypermobility suggestive of mild classic EDS.[14] This may indicate that some cases of keratoconus are associated with collagen or another connective tissue element gene defect even if they are not within the scope of EDS.

The case presented is consistent with classic EDS (I), although typing is not certain from the clinical features. Genetic testing was not performed since this would not have altered case management. Limbus-to-limbus corneal thinning has been demonstrated in 2 EDS cases using ultrasound pachymetry; 1 had a central thickness of 419 μm in the right eye and 486 μm in the left eye and a minimum peripheral thickness of 388 μm and 389 μm, respectively, and 1 had a central thickness of 400 μm and 455 μm in the right eye and left eye, respectively, and a minimum peripheral thickness of 394 μm and 400 μm, respectively.[9] Our case illustrates the advantage of Orbscan measurement and documentation of corneal thinning. Although this case demonstrates that very thin corneas can be stable, EDS remains an absolute contraindication to LASIK.

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