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Title: Orbscan Mapping in Ehlers-Danlos Syndrome

Short running head: Ehlers-Danlos Orbscan

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Abstract

A candidate for refractive surgery presented with classic (type I) Ehlers-Danlos syndrome. While surgery was not offered, clinical examination revealed blue sclera, limbus-to-limbus corneal thinning, myopia and astigmatism. Orbscan pachymetry mapping provided a striking demonstration of limbus-to-limbus thinning with central corneal thickness of R 360 μm and L 383 μm and mid-peripheral corneal thickness ranging from R 370 to 438 μm and L 376 to 434 μm. Interestingly, despite the theoretical biomechanical weakness from both thin cornea and defective collagen, regular surface topography is maintained without the development of keratoconus. While all types of Ehlers-Danlos syndrome remain an absolute contraindication to laser refractive surgery, Orbscan mapping provides a valuable insight into corneal shape and thickness in this condition.

Setting

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Synopsis

Orbscan pachymetry mapping is a useful tool for demonstrating limbus-to-limbus corneal thinning in Ehlers-Danlos syndrome.
Introduction

All types of Ehlers-Danlos syndrome (EDS) are widely accepted as contraindicating laser refractive surgery. The earlier numerical classification of Ehlers-Danlos syndrome has recently been collapsed into 6 distinct clinical types through the addition of molecular and biochemical criteria for diagnosis. In adopting the new classification, the old typing follows in brackets e.g. Classical (I, II), Hypermobility (III), Vascular (IVa, IVb, IVc), Kyphoscoliosis (VI, Vla, Vlb), Arthrochalasis (VIIa, VIIb) and Dematosparaxis (VIIc). Note that the former EDS types V (2 families reported), VIII (a few families reported) and X (one family reported) have been removed to an “others” category and type IX is no longer considered to be an EDS phenotype. While the molecular basis of EDS is heterogeneous, there are three fundamental mechanisms of disease known to produce EDS: 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 this abnormal collagen strength that contraindicates laser refractive surgery, as the risk of post-surgical ectasia is presumed higher and the risk of devastating intra-operative complication like globe rupture is possible. Herein the clinical findings of a case of classic EDS (I), presenting for laser refractive surgery.

Case report

A 54-year-old female presented for LASIK refractive surgery. She had previously tried contact lenses but had never been able to be successfully fit, citing discomfort with both hard and soft contact lenses. She was particularly keen to be spectacle free for thespian activities. She volunteered the diagnosis of Ehlers-Danlos syndrome type
I, which she believed did not affect her eyes. Her health was otherwise unremarkable, with hormone replacement therapy being the only medication. Glasses were worn for short sightedness since the age of 10, but she claimed that her prescription had been stable over many years. She wore varifocals of strength R –3.00 / -1.50 x 158, L – 5.50 / -1.00 x 28 and add +2.00 D. Refraction yielded no change with corrected visual acuity of R 6/4.8- L 6/4.8 and N4. Scotopic pupil sizes were 4.50 mm R + L and intraocular pressures were 14 mmHg R + L. Slit lamp examination revealed blue sclera, clear but thin corneae and otherwise normal anterior and posterior (no angioid streaks) segments. Retinoscopy reflexes were regular and no findings suggestive of keratoconus noted. Orbscan II topography demonstrated a normal anterior float and regular topography with 1.50 D of with-the-rule astigmatism in each eye (Figure 1). The corneal curvatures were within normal limits with simulated keratometry of R 43.5 x 45.0 D and L 44.1 x 45.1 D. However, the pachymetry maps were striking with central corneal thickness of R 360 μm and L 383 μm and mid-peripheral corneal thickness ranging from R 370 to 438 μm and L 376 to 434 μm. Ultrasound pachymetry confirmed that the corneae were unusually thin although the measurements were significantly greater than Orbscan with central corneal thickness of R 440 μm and L 439 μm. The acoustic adjustment factor for the Orbscan was set at 0.92 although this only explains half of the discrepancy between the two measurements. Orbscan minimum corneal thickness measurements were R 318 μm and L 323 μm, which corresponded to points of maximum posterior elevation R 2.3 and L 2.6 mm below the corneal centre. Posterior elevations were unusually high with maxima of approximately R 65 and L 80 μm. The patient was denied LASIK refractive surgery.
Discussion

The cardinal features of Ehlers-Danlos syndrome are hyperextensible skin, hypermobile joints, easy bruisability and fragility of connective tissues leading to a variety of clinical manifestations. However, these features vary depending upon the specific type of EDS. The demonstration of cutaneous hyperextensibility, as opposed to lax or redundant skin, is tantamount to diagnosing EDS, but minimal elasticity of the skin also occurs. Probably more than half of all patients with unequivocal signs cannot be fit easily into the classification system, and as more biochemical studies are completed, it is likely that the classification will change. Classical EDS (I, II) is characterised 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 the classical EDS (I, II) phenotype (25-45% of individuals), other mutations may play a role, including in the tenascin X gene. Hypermobility EDS (III) is characterised by joint hypermobility, pain, dislocations, no skin scarring, and autosomal dominant inheritance but the gene defect is unknown. Vascular EDS (IV) is characterised by thin 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. Kyphoscoliosis EDS (VI) is characterised by hypotonia, joint laxity, hyperextensible skin, congenital scoliosis, ocular fragility and autosomal recessive inheritance. Five different mutations of the PLOD1 (lysyl hydroxylase 1) gene have been described in kyphoscoliosis EDS. Arthrochalasia EDS (VIIa&b) is characterised by severe joint hypermobility, congenital hip dislocation, mild skin hyperextensibility, scoliosis, bruising and autosomal dominant inheritance. This usually results from loss of the
substrate sequence for the N-terminal procollagen protease in one of the chains of type I procollagen. Dermatosparaxis EDS (VIIc) is characterised 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.

Even though 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, but the existence of corneal thinning and keratoconus 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. Also reported are limbus-to-limbus corneal thinning, lens subluxation, angioid streaks, retinal detachment, and macular degeneration. Corneal findings include keratoconus e.g., keratoglobus e.g., cornea plana, posterior keratoconus, corneal opacity, and microcornea. Acute hydrops has been reported in patients with Ehlers-Danlos syndrome and keratoconus or keratoglobus, but not without either. Ocular fragility where the corneal ruptures with minimal trauma has been reported in 7 of 11 cases in one series. However, this only occurs in kyphoscoliosis (VI) EDS. This type is uncommon with only 50 or so cases having
been reported e.g.,17-19 and was previously called ocular-scoliotic type (type VI) because it was considered to be characterised by ocular findings disproportionate to systemic findings, but ocular complications are not always present. Keratoconus, blue sclera, lens subluxation or retinal detachment 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, VI) found no cases with slit-lamp or retinoscopy findings suggestive of keratoconus.20 Only one case had asphericity and profile difference maps suggestive of mild keratoconus, but no cases had I-S values greater than the 1.60 threshold.21 The apparent rarity of keratoconus in Ehlers-Danlos syndrome despite collagen deficiencies likely to give “weak” corneae and, if our case is typical, thin corneae is interesting. That regular corneal topography is maintained despite these risk factors for keratoconus suggests that a cofactor or precipitating event is required to trigger ectasia is these eyes. Whilst keratoconus may be rare in Ehlers-Danlos syndrome, one series of 44 keratoconus cases was found to have 22 cases with joint hypermobility suggestive of mild classical EDS.14 This may suggest that some cases of keratoconus are associated with collagen or other connective tissue element gene defect even if not within the scope of EDS.

The case presented is consistent with classic EDS (I), although typing is not certain from clinical features, but genetic testing was not performed since this would not have altered case management. Limbus-to-limbus corneal thinning has been demonstrated in two EDS cases previously using ultrasound pachymetry, one with central thickness of R 419 μm L 486 μm and minimum peripheral thickness or R 388 μm L 389 μm, the other with central thickness of R 400 μm L 455 μm and minimum peripheral thickness
of R 394 μm L 400 μm.9 Our case illustrates the advantage of Orbscan measurement and documentation of corneal thinning. While this case demonstrates that very thin cornea can be stable, EDS remains an absolute contraindication to LASIK.

References


Legends for Figures

Figure 1.

a. Orbscan map of the right eye and b. of the left eye.