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COMMENTARY

Potential Risks of Corneal Refractive Surgery in Patients with Ectodermal Dysplasia

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ABSTRACT

Ectodermal dysplasia (ED) involves the aberrant development of at least two ectodermal derivatives, such as skin, teeth, hair, sweat glands, and ocular tissue. The group of over 200 conditions is commonly classified into two major types: hypohidrotic/anhidrotic ED, in which sweat glands are either absent or significantly reduced, and hidrotic ED, in which sweat glands are normal. Ocular manifestations pertinent to patients undergoing corneal vision correction surgery include multifaceted dry eye syndrome, corneal pathology, such as recurrent erosions, scars, neovascularization, and limbal stem cell deficiency, and early-onset cataracts and glaucoma. In this article we discuss the current understanding of ED and offer factors to consider when these patients are seeking corneal refractive surgery.

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Key Summary Points

Ectodermal dysplasia (ED) involves the aberrant development of at least two ectodermal derivatives, such as skin, teeth, hair, sweat glands, and ocular tissue. The group of over 200 conditions is commonly classified into hypohidrotic/anhidrotic ED and hidrotic ED 2 on the basis of sweat gland involvement

Eyelid dysmorphology and meibomian gland atresia, aplasia, or obstruction can lead to evaporative dry eye and faster tear film breakup time in patients with ED, which increases the risk of corneal infection and refractive instability. It is more likely that this population will have multifactorial ocular surface dryness requiring aggressive dry eye management with topical cyclosporine, a slow taper of topical steroids, punctal plugs, or autologous serum

Corneal changes in ED including erosions, vascularization, pannus, scarring, ulcers, perforation, and limbal stem cell deficiency (LSCD) are caused by recurrent infections of the eyelid margins, defective tear film formation, and primary dysplasia of the corneal epithelium. This leads to decreased reliability of topographical measurements preoperatively, an increased risk of intraoperative complications during LASIK, PRK, or SMILE, and a greater likelihood of encountering postoperative complications of delayed corneal wound healing, including infectious keratitis and epithelial ingrowth

Even with subclinical meibomian gland dysfunction and LSCD, this population may be especially vulnerable to dry eye syndrome and complications of delayed corneal wound healing that could result in poor visual outcomes and patient dissatisfaction

Ectodermal dysplasias (EDs), including more than 200 different disorders, involve at least two ectodermal derivatives, such as skin, teeth, hair, sweat glands, and ocular tissue [1, 2]. However, with an estimated incidence of 7/10,000 births [3], it is considered a relatively rare disease entity. The classification system of ED is quickly evolving as researchers are continuing to find molecular-genetic pathophysiology. Currently, 80 of the approximately 200 conditions have known genetic links [4]. However, for clinical diagnosis and consideration, phenotypic classification is commonly characterized by two subgroups: hypohidrotic/anhidrotic ED (HED) and hidrotic ED 2 (HED2) [5]. Table 1 summarizes the classification of ED and includes subtypes with previously reported ocular findings. HED is the more prevalent subgroup and its X-linked variety (XLHED) is much more common than the various autosomal subtypes [6, 7]. XLHED affects more male individuals than female individuals [8] and often presents as severe neonatal heat intolerance, leading to findings of hypoplasia/aplasia of the eccrine sweat glands, hair follicles, and teeth, as well as craniofacial abnormalities and periorbital pigmentation early in life [1]. The lack of eccrine sweat glands (sebaceous, submucosal, lacrimal, salivary, mammary, and meibomian glands) can result in obstructive airway conditions, atrophic rhinitis, recurrent respiratory infections, keratoconjunctivitis sicca, chronic eczema and other skin conditions, and breastfeeding difficulties [9]. With these many complications, mortality approaches 30% by 3 years of age, although for survivors of this period life expectancy is normal [3]. Milder forms of HED can be found in male and female individuals with autosomal dominant forms and in female carriers of XLHED, often leading to a definitive diagnosis much later in life [10]. Similarly, HED2 (Clouston syndrome) follows autosomal dominant inheritance, but mostly occurs in the French-Canadian population [11, 12]. Unlike HED, HED2 usually spares the sweat glands and teeth, and its ocular manifestations are typically limited to a sparsity of eyebrows and eyelashes (madarosis) [13]. With such a wide variety of phenotypic presentations, patients with ED seeking vision correction surgery for refractive error may present with relatively few obvious ocular symptoms. Therefore, it is important for ophthalmologists to be familiarized with ED and the associated ocular findings in this population.

Ectoderm gives rise to many components of the eye and associated orbital structures, with some contributions from the mesoderm. Neuroectoderm forms the retina, epithelial lining of the ciliary body and iris, and optic nerve. Surface ectoderm forms the lens and corneal epithelium, as well as the skin, hair follicles, and glands of the eyelid. Neural crest cells, which are also ectoderm-derived, give rise to Descemet's membrane, sclera, endothelium of the cornea, orbital bones, and connective tissue. Mesoderm then contributes to the vitreous body, suspensory fibers, Bowman's layer and stroma of the cornea, blood vessels of the eye (including scleral and corneal), extraocular muscles, and muscles of the eyelid [14, 15]. With this significant embryologic contribution to eye structures, it is understandable that ED can lead to the numerous ocular abnormalities summarized in Table 1.

Table 1 Ectodermal dysplasias with reported ocular findings. Adapted from Wright JT, Fete M, Schneider H, et al. Ectodermal dysplasias: Classification and organization by phenotype, genotype and molecular pathway. Am J Med Genet A. 2019;179:442–7

Subgroup	Subtypes	Gene	Inheritance pattern	Ocular findings	Other phenotypic manifestations
Hypohidrotic/ anhidrotic (HED)	X-linked (XLHED); Christ-Siemens-Touraine syndrome	*Ectodysplasin A (EDA)*	X-linked	Periorbital pigmentation [1], keratoconjunctivitis sicca [3, 9], sparse eyebrows/eyelashes, conjunctivitis [9]	Hypohidrosis, hypotrichosis, hypodontia, craniofacial dysmorphology [1], eczematous skin, growth retardation, supernumerary nipples [9]
	Hypohidrotic ectodermal dysplasia 10A	*Ectodysplasin A receptor (EDAR), EDAR-associated death domain (EDARADD)*	Autosomal dominant (AD) [7, 31] Autosomal recessive (AR) [7, 31]	Periorbital pigmentation	Hypohidrosis, hypotrichosis, hypodontia, smooth dry skin, craniofacial dysmorphology
	Hypohidrotic ectodermal dysplasia 10B	*EDAR, EDARADD*	AD, AR [7, 31]	Periorbital pigmentation	Hypohidrosis, hypotrichosis, hypodontia, smooth dry skin, craniofacial dysmorphology
	Onycho-odonto-dermal dysplasia (OODD)	*Wingless-type 10A (WNT10A)*	AR [31]	Sparse eyebrows	Severe hypodontia, smooth tongue, hyperhidrosis, hyperkeratosis, dystrophic nails, thin hair
	Schöpf-Schulz-Passarge syndrome	*WNT10A*	AR [31]	Eyelid cysts	Hypodontia, keratoderma, hypoplastic nails, hypotrichosis
	Ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome 3 (EEC3)	*Tumor protein p63 (TP63)*	AD [32]	Blepharophimosis [1], lacrimal gland aplasia, keratoconjunctivitis [32], photophobia, punctal agenesis, dry eye, blepharitis, ptosis, amblyopia [2], corneal pannus/neovascularization [25, 26]	Cleft lip/palate, microdontia, hypodontia, syndactyly, hypokeratosis, nail dysplasia, hypotrichosis [1], hypospadias [32]
	Ankyloblepharon, ectodermal deficits, cleft lip/palate (AEC, Hay-Wells) syndrome	*TP63*	AD [32]	Lacrimal duct atresia, ankyloblepharon [1, 32], sparse eyebrows/eyelashes [32], strabismus, punctal agenesis, dry eye, trichiasis, ptosis, amblyopia, photophobia [2]	Scalp/skin erosions, conductive hearing loss, maxillary hypoplasia, hypotrichosis, cleft lip/palate, hypodontia [1, 32], erythroderma, alopecia, trismus, syndactyly, poor weight gain [32]
	Rapp-Hodgkin syndrome [32]	*TP63* [32]	AD [32]	Lacrimal duct atresia, ankyloblepharon [32], photophobia, punctal agenesis, dry eye [2]	Scalp/skin erosions, alopecia, erythroderma, hypopigmentation, hypotrichosis, nail dystrophy, hypodontia, cleft lip/palate, maxillary hypoplasia, micrognathia, trismus, conductive hearing loss, syndactyly, poor weight gain [32]
	Acro-dermato-ungual-lacrimal-tooth (ADULT) syndrome	*TP63*	AD [32]	Lacrimal duct atresia, sparse eyebrows/eyelashes [32]	Hypodontia, nipple hy/nipple hypoplasia, dry skin, nail dysplasia, syndactyly [32]

Table 1 continued

Subgroup	Subtypes	Gene	Inheritance pattern	Ocular findings	Other phenotypic manifestations
	Limb mammary syndrome	*TP63*	AD [32]	Lacrimal duct atresia	Hypodontia, hypoplastic breasts, syndactyly, ectrodactyly, nail dysplasia [1], cleft lip/palate [32]
	Incontinentia pigmenti	*Inhibitor of kappa light polypeptide gene enhance in B cells (IKBKG)*	X-linked [5]	Cataract, microphthalmia	Short stature, hypodontia, extra ribs, breast aplasia, staged skin involvement, nail dystrophy, atrophic hair [1], thorax abnormalities [17]
	Ectodermal dysplasia 4, hair/nail type (ECTD4)	*Keratin 85 (KRT85)*	AR [13]	Absent eyebrows/eyelashes	Nail dystrophy, onycholysis, alopecia, normal skin/teeth
	Arthrogryposis and ectodermal dysplasia	Unknown [5]	AR [5]	Cataract	Short stature, microcephaly, cleft lip/palate, oligodontia, enamel defects, arthrogryposis, hypohidrosis, onychodysplasia
	Ectodermal dysplasia, ectrodactyly, and macular dystrophy syndrome; EEM	*Cadherin 3 (CHD3)*	AR [5]	Sparse eyebrows/eyelashes, macular dystrophy	Sparse scalp hair, hypodontia, small teeth, ectrodactyly, syndactyly, camptodactyly, normal sweating
	Oculo-ectodermal (Toreillo-Lacassie-Droste) syndrome [2]	*Kirsten rat sarcoma viral oncogene homolog (KRAS)* [2]	Unknown [2]	Ptosis, amblyopia, posterior embryotoxon, choroidal osteoma, peripapillary colobomas, epibulbar dermoid, strabismus, astigmatism, hyperopia, corneal opacity, acrochordon, microphthalmia, chorioretinal atrophy [2]	Cutis aplasia, growth failure, lymphedema, cardiovascular defects, neurodevelopmental deficits, bony tumors [2]
	Keratitis-ichthyosis-deafness syndrome [13]	*Gap junction protein beta-2 (GJB2)* [13]	AD [13]	Photophobia, corneal ulceration, corneal scarring [13]	Sensorineural deafness, progressive hyperkeratotic plaques, palmoplantar hyperkeratosis, sparse hair, nail dystrophy [13]
	Marshall syndrome [2, 33]	*Collagen type 11 alpha 1 chain (COL11-A1)* [2, 33]	AD [33]	High myopia, glaucoma, retinal detachment [33], cataract [2, 33]	Spondyloepiphyseal dysplasia, stunted growth, osteoarthritis, central facial dysmorphia, cleft palate, sensorineural deafness [33]
Hidrotic (HED 2)	Clouston syndrome [13]	*Gap junction protein beta-6 (GJB6)* [13]	AD [13]	Sparsity of eyebrows/eyelashes [13]	Alopecia, nail dystrophy, palmoplantar hyperkeratosis, cutaneous hyperpigmentation, finger clubbing, spares sweat glands and teeth [13]

Table 2 Recommended clinical testing, examinations, and potential findings for patients with ectodermal dysplasia seeking corneal refractive surgery

Region	Potential findings	Testing
Globe	Microphthalmia [1, 2]	External examination, slit lamp exam
	Strabismus [2, 34]	Refraction
	Hyperopia [2]	
	High myopia [33]	
	Photophobia [2]	
Eyelid	Ankyloblepharon [1, 2, 7, 26]	External examination, slit lamp exam
	Skin tags (acrochordon) [2]	Meibography, meibomianoscopy
	Trichiasis [7], trichomegaly [35]	Lacrimal duct probing with irrigation
	Loss of eyelashes/eyebrows (madarosis) [1, 2, 7, 26]	
	Ptosis [2], ectropion, entropion [18]	
	Blepharitis, dacryocystitis [2, 7]	
	Lacrimal duct atresia/obstruction [1, 2, 25]	
	Meibomian gland hypoplasia/aplasia [2, 7, 35]	
	Nasolacrimal duct atresia [2, 7, 19]	
Cornea	Astigmatism [2]	Refraction
	Reduced tear production [7]	Tear meniscus height
	Defective tear film [25, 26]	Tear film break-up time (TBUT)
	Keratoconjunctivitis sicca [13]	Schirmer's testing
	Dryness, erosion, ulceration, scarring, opacity [7, 25, 26]	Fluorescein, Lissamine green dyes
	Vascularization, pannus [19, 26]	Corneal OCT
	Epibulbar dermoid [2]	Confocal microscopy
	Keratitis [18], superficial punctate keratitis [9]	Impression cytology
	Posterior embryotoxon [2]	
	Limbal stem cell deficiency [22, 26]	
Lens	Early-onset cataract [1, 25, 28, 29, 33]	Slit lamp exam
		Scheimpflug densitometry
		Brightness acuity test (BAT)
Optic nerve	Peripapillary coloboma, optic nerve coloboma [2]	Indirect ophthalmoscopy
	Early-onset glaucoma [20, 30, 33]	Optic nerve OCT

Table 2 continued

Region	Potential findings	Testing
Retina	Retinal vein tortuosity [35]	Indirect ophthalmoscopy
	Posterior pole osteomas [2]	Retinal OCT
	Chorioretinal atrophy [2]	Fluorescein angiography
	Retinal detachment [33]	

OCT optical coherence tomography

Refractive error has been found in up to 43% of patients with ED [2], making it likely that these patients will seek corneal refractive surgery (CRS). In this population, it is important to evaluate for ocular surface inflammatory disease, corneal pathology including recurrent erosions, stromal scars, neovascularization, and limbal stem cell deficiency (LSCD), and early-onset cataracts and glaucoma. Table 2 references recommended testing with potential findings that have previously been reported in cases of ED.

Knowing that transient ocular surface dryness is common following laser in situ keratomileusis (LASIK), photorefractive keratectomy (PRK), and small lenticule extraction (SMILE) procedures [16], physicians should be aware of an increased risk of dry eye symptoms for patients with ED. During screening examination, ophthalmologists may find defective tear film formation and reduced tear production caused by lacrimal and meibomian gland atresia, aplasia, or obstruction that are common with ED [9, 17–20]. In addition, this population is prone to craniofacial and eyelid dysmorphology, such as ankyloblepharon, trichiasis [7], and ectropion [18], that can further promote ocular surface irritation and dryness. Depending on the severity, these abnormalities may require multidisciplinary consultation, including oculoplastics. With this multifactorial pathophysiology for dry eye, it is more likely that patients with ED will necessitate aggressive management with topical cyclosporine, a slow taper of topical steroids, punctal plugs, and autologous serum. Patients must understand that dry eye syndrome (DES) carries an increased risk of refractive instability, postoperative infectious keratitis [21], and exacerbated symptoms of corneal dryness following CRS.

Since the cornea is partially derived from ectoderm, ED can also cause primary corneal dysplasia, such as LSCD [22]. The limbal stem cells replenish the corneal epithelium and inhibit the infiltration of conjunctival epithelial cells onto the cornea [23]. After LASIK, SMILE, or PRK, patients with ED with LSCD can have a higher risk of delayed epithelial healing and turnover, neovascularization, and pannus [24] resulting in corneal opacification and reduced visual acuity [23]. Furthermore, glandular abnormalities associated with ED contribute to recurrent infections of the eyelid margins and deficient tear film formation that can exacerbate underlying corneal erosions and vascularization leading to corneal ulcers, scarring, or even perforation [7, 25, 26]. Preoperatively, defective tear film formation can decrease the reliability of topographical measurements at the time of refractive screening [27]. Intraoperatively, stromal scars can increase the risk of vertical gas breakthrough during femtosecond flap creation for LASIK, and bleeding into the stroma secondary to pannus and vascularization can complicate excimer laser ablation. Postoperatively, LSCD along with pannus and blood reaching the flap interface can increase the risk of inflammatory reactions, such as diffuse lamellar keratitis and epithelial ingrowth [21]. Therefore, ophthalmologists should pay particular attention to the cornea and glands of patients with ED, who are seeking vision

correction surgery, and inform them of these increased risks.

Ophthalmologists should also have a high suspicion for other common ocular abnormalities associated with ED including early-onset cataracts [28, 29] and glaucoma [20, 30]. Evaluation for these conditions may necessitate specialized imaging, such as Scheimpflug densitometry to assess for low-grade cataracts and optical coherence tomography to assess the optic nerve, especially in patients found to have elevated intraocular pressure during their screening examination.

In conclusion, for patients with ED seeking CRS, special consideration must be made to determine the extent of eyelid dysmorphology, glandular dysfunction, and corneal pathology, such as recurrent erosions, scars, neovascularization, and LSCD, associated with their disease. These conditions could potentiate intraoperative complications and unfavorable postoperative outcomes. Even with subclinical meibomian gland dysfunction and LSCD, this population may be especially vulnerable to DES and unpredictable corneal wound healing. Patients with ED that are considered candidates for CRS will need to be fully informed that their disorder carries increased risks that may necessitate substantial prophylactic measures beyond that of an average refractive surgery patient. In current scientific literature, there is abundant information on ED as a disease entity, but there are no reports concerning the outcomes of CRS in this patient population. Therefore, these recommendations are based on the most common clinical findings of ED. However, with such a wide variety of possible presentations, every patient with ED should be thoroughly evaluated concerning candidacy for corneal refractive surgery at the discretion of their ophthalmologist.

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