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COMMENTARY

Implications of Corneal Refractive Surgery in Patients with Fabry Disease

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ABSTRACT

Fabry disease is an X-linked lysosomal storage disorder involving abnormal metabolism of glycosphingolipids, resulting in a range of multisystem organ dysfunction and ocular manifestations. Reports of laser-assisted in situ keratomileuses (LASIK) and photorefractive keratectomy (PRK) are lacking in this patient population. Proceeding with corneal refractive surgery in patients with Fabry disease raises concerns regarding the pre-existing corneal manifestations, reduced mesopic visual acuity, the potential for conjunctival lymphangiectasia, and predisposition to dry eye syndrome. This commentary discusses the current understanding of Fabry disease, including its ocular manifestations, and explores factors to consider when evaluating these patients for LASIK or PRK.

Keywords: Fabry disease; LASIK; PRK; Vortex keratopathy; Cornea verticillata; Glycosphingolipids

Key Summary Points

The most common ocular manifestations of Fabry disease are bilateral cornea verticillata and vortex keratopathy.

Proceeding with corneal refractive surgery in patients with Fabry disease raises concerns regarding the pre-existing corneal manifestations, reduced mesopic visual acuity, the potential for conjunctival lymphangiectasia, and predisposition to dry eye syndrome.

Evaluation of a patient with Fabry disease should include a thorough slit lamp examination, as well as brightness acuity testing, corneal confocal microscopy, corneal sensitivity testing, and corneal densitometry analysis.

Due to the unknown interaction between Fabry disease and laser vision correction, we suggest counseling against corneal refractive surgery in patients with Fabry disease.

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Patients with Fabry disease may present to your clinic requesting evaluation for corneal refractive surgery. Despite the abundance of knowledge about Fabry disease, there is a paucity of literature reporting cases of laser-assisted in situ keratomileusis (LASIK) or photorefractive keratectomy (PRK) in this patient population. Additionally, there are no formal recommendations regarding corneal refractive surgery in these patients. The present article reflects on the current understanding of Fabry disease, including its ocular manifestations, and explores factors to consider when evaluating a patient with Fabry disease for potential LASIK or PRK. It is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Fabry disease is an X-linked lysosomal storage disorder in which abnormal metabolism of glycosphingolipids results in multisystem organ dysfunction. The estimated incidence of Fabry disease is 1 in 117,000 live births [1]. Hundreds of mutations in the galactosidase alpha (*GLA*) gene have been identified in association with Fabry disease, resulting in a wide range of symptom severity [2]. Systemic manifestations of Fabry disease include but are not limited to dysesthesia, hypohidrosis, angiokeratomas, cardiomyopathy, cerebrovascular disease, progressive neuropathy, and nonspecific gastrointestinal disturbances [2]. Even within families, the presentation of Fabry disease is variable [2].

Specific ocular manifestations result from progressive deposition of glycosphingolipids in the cornea, lens, and ocular vessels. The most characteristic ocular finding is bilateral cornea verticillata, or vortex keratopathy, which can be observed on slit-lamp examination as early as 6 months of age and is often the first sign of disease [3]. These white to yellow–brown whorls have been reported in almost all men and up to 90% of women with Fabry gene mutations [3], though the presence of cornea verticillata appears to be independent of disease severity [4]. The formation of vortex keratopathy is hypothesized to adhere to the XYZ hypothesis of corneal epithelial regeneration, in which limbal stem cells migrate centripetally to the central cornea to replace desquamating epithelial cells [5, 6]. Presumably, when laden with lipid, these migrating stem cells create the whorl-like streaks seen in Fabry disease, which follow the vortex of a normally regenerating cornea.

Although most patients with cornea verticillata due to Fabry disease have normal visual acuity compared to healthy controls, there is a documented decrease in contrast sensitivity and an increase in stray light [7]. Additionally, patients with Fabry disease subjectively report more difficulty with night vision and glare symptoms [8]. Given that corneal refractive surgery can promote nighttime glare and decreased contrast sensitivity, patients with Fabry disease who already have these symptoms at baseline may be unsatisfied with their visual outcomes from LASIK or PRK.

Cornea verticillata has also been shown to change over time. One case series reported at least mild evolution of verticillata in all corneas on comparative imaging over 18 months of observation, even in patients on stable enzyme replacement therapy [3]. These changes were usually only related to the corneal appearance rather than the intensity or clinical significance of the vortex keratopathy. However, these changes show that corneal findings are not static over time in Fabry disease, even with good disease control. Considering the dynamic nature of the cornea in Fabry disease, performing surgical correction to the cornea may result in unpredictable postoperative outcomes.

In addition to causing cornea verticillata, the abnormally metabolized glycosphingolipids are thought to deposit in the nerve ganglia or lacrimal gland [8]. Furthermore, lysosomal accumulation of glycosphingolipids has been shown to lead to atrophy of small unmyelinated nerves like those of the cornea [2]. Taken together, these pathophysiologic processes may explain the high rates of dry eye syndrome observed in patients with Fabry disease [3]. When considering corneal refractive surgery in this patient population, it is important to remember the well-known incidence of dry eye syndrome after corneal refractive surgery, even in healthy corneas. Specifically in LASIK, mechanical injury to corneal nerves secondary to flap creation minimizes corneal sensitivity, thus blocking reflex tear secretion [9]. Studies evaluating the administration of murine nerve

growth factor after LASIK in rabbits suggest the importance of nerve integrity for minimizing postoperative dry eyes and thus optimizing postoperative corneal healing [9]. Considering that patients with Fabry disease may not have a robust population of healthy corneal nerve fibers and often have dry eye disease at baseline, these findings may be relative contraindications for corneal refractive surgery [10].

The conjunctival architecture should also be evaluated in a patient with Fabry disease seeking consultation for corneal refractive surgery. Conjunctival lymphangiectasia, which presents as cysts and dilations, has been observed in Fabry disease, even in patients on enzyme replacement therapy [11]. This conjunctival edema would prevent the formation of an adequate suction seal for corneal laser procedures. Specifically in LASIK, suction loss can result in incomplete flap formation, and patients should be screened preoperatively for risk factors that would impede adequate suction [12]. Furthermore, redundant conjunctiva can further exacerbate ocular surface disease, thus compounding dry eye symptoms [11].

Other limitations to best corrected visual acuity in patients with Fabry disease include anterior subcapsular cataract, posterior subcapsular cataract (also known as a Fabry cataract), and corneal haze [13]. Fabry disease can also be associated with retinal vessel tortuosity, though vessel wall integrity is usually preserved.

Given the wide range of ocular manifestations, any patient with Fabry disease seeking corneal refractive surgery should undergo a thorough evaluation, including testing beyond the scope of a standard LASIK or PRK evaluation (Table 1). Visual acuity testing should be

Table 1 Examinations and tests to perform as part of a thorough evaluation for corneal refractive surgery in a patient with Fabry disease, and the possible associated findings

Examination or test	Possible finding
Visual acuity	
Photopic visual acuity	Usually normal
Mesopic visual acuity	Decreased
brightness acuity test	Increased glare
Slit lamp examination	
Conjunctiva	Conjunctival lymphangiectasia
Cornea	Cornea verticillata
	Haze
	Ocular surface disease, including superficial punctate keratitis
Lens	Anterior subcapsular cataract
	Posterior subcapsular (Fabry) cataract
Fundoscopy	
Retinal vessels	Tortuosity
	Hemorrhage (uncommon)
Corneal confocal microscopy	Decreased nerve fiber density
	Decreased nerve branch density
Non-contact corneal aesthesiometry	Decreased corneal sensitivity
Scheimpflug optical assessment	Increased corneal density

performed in both photopic and mesopic conditions, with the addition of brightness acuity testing, to establish a preoperative baseline of night and glare symptoms and better understand the postoperative potential. Slit-lamp examination allows assessment of any of the ocular manifestations of Fabry disease discussed above. Corneal confocal microscopy (CCM), a non-invasive method to visualize nerve fibers directly, is a useful adjunctive evaluation to characterize Fabry-associated neuropathy. Studies of patients with Fabry disease found decreased corneal nerve fiber and branch density on CCM [14, 15]. This was associated with reduced corneal sensitivity on non-contact corneal aesthesiometry. Lastly, corneal densitometry analysis with Scheimpflug technology can objectively quantify corneal haze [16].

To our knowledge, no case reports of LASIK or PRK in a patient with Fabry disease have been documented in the literature. Even reports of LASIK in other keratopathies, such as amiodarone-induced cornea verticillata, are lacking. There is a report of LASIK in a patient with partial limbal stem cell deficiency secondary to contact lens overuse, and this patient had a whorl epitheliopathy that shares some features with Fabry verticillata [17]. Successful completion of LASIK in this patient offers encouragement that corneal refractive surgery can sometimes be performed in patients with a suboptimal corneal surface. However, a lack of precedent makes it difficult to determine if LASIK and PRK can safely be performed in the setting of Fabry disease. The corneal manifestations, reduced mesopic visual acuity, potential for conjunctival lymphangiectasia, and predisposition to dry eye syndrome could result in unpredictable and unsatisfactory postoperative refractive outcomes. Due to the unknown interaction between Fabry disease and laser vision correction, we suggest counseling against corneal refractive surgery in patients with Fabry disease. In the case of a persistent patient who is highly motivated to obtain freedom from glasses and contact lenses, the surgeon and patient must have a detailed discussion about the potential risks and lack of documented outcomes. If proceeding with corneal refractive surgery, the surgeon should consider publishing postoperative results for more definitive risk counseling to be developed.

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