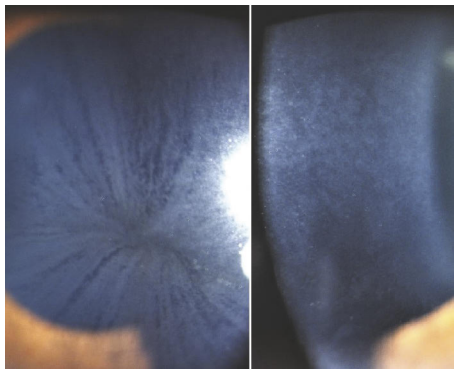
Identify Fabry Disease Earlier

LOOKING FOR QUINTESSENTIAL cornea verticillata in patients suspected of Fabry disease? Evidence suggests Fabry keratopathies aren't as textbook or as prominent as often portrayed, with eye doctors potentially missing crucial warning signs of a life-changing disease when scanning corneas for prominent whorls.

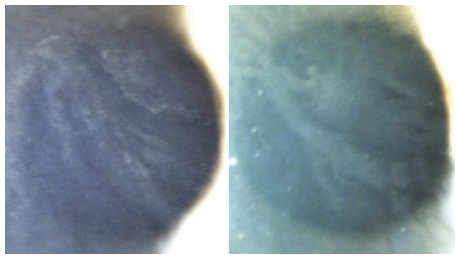
Published in the *British Journal of Ophthalmology*, a recent investigator-initiated study detailed how Fabry keratopathies not only manifest in great variety—sometimes with no characteristic whorl at all—and with additional amorphous features but also change over time and differ between right and left eyes of the same individual. Knowledge of such evidence could help eye care practitioners better identify the disease earlier—and get patients appropriate specialty care sooner.

A rare, inherited X-linked lysosomal storage disorder created by faulty glycolipid metabolism, Fabry disease is characterized by the continuous buildup of unmetabolized globotriaosylceramide (Gb3), resulting in cell abnormalities and organ dysfunction. With two major disease phenotypes—type 1 "classic" with little or no α-galactosidase A (α-Gal A) enzyme function and childhood onset with most severe disease, and type 2 "late onset" with only residual 1-15% α-Gal A activity and midlife onset with variable disease—both Fabry types can lead to progressive kidney damage, cardiac disease and early death if left untreated.

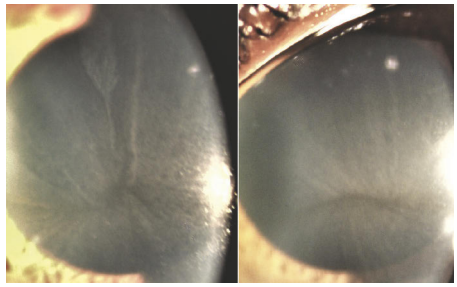
Previous estimations suggest that Fabry disease affects 1 in 40,000 to 60,000 males and an unknown prevalence among females, but more recent studies show that late onset may be up to 16 times more prevalent in both males and females. Fabry disease's earliest observable manifestation is often a bilateral keratopathy resulting from lipid inclusions of Gb3 in the basal and surface corneal epithelial cells and epithelial basement membrane. Fabry keratopathy is found in over 99% of men and up to 90% of women with classic forms of the disease; however, there is great variance in even the most marked keratopathies and changes over time, which are what the optometric clinical researchers at the University of Alabama at Birmingham (UAB) sought to detail.



A quintessential Fabry whorl of one patient, on the left, and central patchiness without a whorl of another patient, at higher magnification, on the right.



Prominent arms from a superonasal corneal vortex cross an undilated pupil, on the left, and as seen again three years later, on the right. Note the change that occurred over time.



Right and left eyes of the same patient, both having inferior corneal whorls in a "mustache" shape. Note the two prominent vertical streams of the right cornea and the similarities and differences between eyes.

The findings

Per the study, researchers analyzed serial biomicroscopic images of keratopathies in five men and five women with classic forms of Fabry disease over an 18-month period, then categorized the keratopathies by changes over time and comparisons between the same individual, family and genotype. Of the subjects, there was one pair of male-female family members with the same genetic mutation (W277X), another male-female family pair with the same mutation (R227X), and one set of two men and one woman of the same family with the same mutation (W236X).

In both eyes of all 10 Fabry patients, researchers documented diffuse haze; however, seven subjects had amorphous patches, nine subjects had vortices (one patient asymmetrically) and four subjects had vertical streams emanating from the superior limbus. Additionally, the keratopathies varied from mild, observable changes to marked changes over the course of the study.

"There can be very large differences between a Fabry patient's right and left eye keratopathies and between the appearances of Fabry keratopathy from one person to the next," says study author William Benjamin, O.D., Ph.D., professor emeritus of optometry and vision science at UAB. "There can be huge variation between one person and another, and variations between right and left eyes range from minimal to extreme, with a spectrum of similarity between. Similarities between right and left keratopathies of the same individuals were imprecise mirror images of each other."

"Even between siblings with the same mutation, there can be completely different clinical manifestations. Asymptomatic females often have more brilliant corneal lesions than more fully affected classic males within the same family. In addition, the centers of most whorls are located mid-peripherally," adds study author Melanie Sivley, O.D., former associate professor at UAB.

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In females, the extent of disease depends on which X chromosome is more fully expressed, Drs. Sivley and Benjamin explain. While a female could have no mutation on one X chromosome, if there's a mutation on the other X, one X could be silenced to varying degrees. Depending on the degree of X inactivation, she could develop the full complement of Fabry disease equal to that of any male. The opposite could occur, too, when the female has greatly attenuated effects of a Fabry mutation, and there is a spectrum of severity between. Consequently, corneal findings are vital to identifying females carrying Fabry disease.

The presence of a whorl isn't guaranteed, Dr. Benjamin notes, but he believes it would be "very rare" not to have some sort of keratopathy with classic Fabry disease. However, keratopathy in late-onset Fabry (ages 30 to 50) may be a different story. There is so much variability genetically that it's harder to connect the dots with non-classic mutations, Dr. Sivley says, as late-onset cases may not show a keratopathy.

"Identifying these patients as early as possible, particularly females with little or no symptomology, is the key to identifying Fabry families and avoiding diagnostic delays," Dr. Sivley says.

1. Read the signs.

Fabry disease causes multi-organ dysfunction that necessitates a lifetime of comprehensive, multidisciplinary treatment and therapies specifically tailored to that individual to promote quality of life. Although early prenatal diagnosis is possible, many classic Fabry patients will be diagnosed as symptoms manifest in childhood with acroparesthesias, angiokeratomas, hypohidrosis, hearing loss, gastrointestinal problems and keratopathy. As a systemic disorder, it's important for doctors of optometry to consider this range of symptomology and refer cases to a specialist, such as a nephrologist or geneticist, for further evaluation and counseling.

"As primary eye care providers, we should correlate ocular and systemic findings," Dr. Sivley says. "The earliest clinical findings in Fabry disease are keratopathies. Unfortunately, these lesions may be missed because we haven't really known what to look for."

2. Consider medications.

For all the importance in identifying these keratopathies, Dr. Benjamin stresses a couple of points: namely, whorls aren't specific to Fabry, and they are usually not as striking as often depicted in articles and from the podium. To the first point, Dr. Benjamin adds that antimalarial medications often used for lupus—and drawing considerable attention for COVID-19, such as chloroquine and hydroxychloroquine—can cause a lookalike Fabry whorl during chronic treatment. Dr. Sivley adds that oftentimes these whorls, when induced by medications, clear up after discontinuation of the drug. However, these medications could be problematic in making a Fabry diagnosis.

3. Keep diversity in mind.

Fabry keratopathies can be easy to miss. Dr. Benjamin notes that images included in this particular study necessitated special slit-lamp lighting for striking depictions—"one in a hundred or thousand" photos—and routine observations in clinical practice won't be as obvious as publications portray.

"Fabry keratopathy is much more diverse, quite different between patients and even eyes of the same patient," Dr. Benjamin says. "It can change over time and, in some cases, streams of Gb3 come down from the superior limbus and feed a more centralized vortex. In some cases, it's mild; in some cases, it's striking. Optometrists should get an idea of how different these presentations can be so they can identify them when they see them." –*Will Pinkston*

the experts

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