Cornea verticillata in Fabry disease: a useful diagnostic tool available exclusively to the ophthalmologist

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ABSTRACT: Cornea verticillata is a very consistent early finding in Fabry disease. It is highly prevalent both in male sufferers and in female carriers and can be used as a highly sensitive and specific tool for the diagnosis of this disease. It is also helpful for early diagnosis in family studies.

No significant relationship has been established between the presence of cornea verticillata and the degree of systemic involvement in Fabry disease. As such, it does not add to the diagnosis any information regarding systemic severity or the possible progress of the disease.

We present the case of a female carrier of the Fabry disease mutation, who, while initially presenting cardiovascular symptoms, was found to have cornea verticillata as the main ophthalmological finding. We review the characteristics of this corneal change which is of great diagnostic value in a disease that can have an inauspicious prognosis if treatment is not initiated early on.

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Fabry disease (FD) is a rare disease entity (between 1/40,000 and 1/400,000 live male births) caused by a hereditary recessive X-linked mutation that produces α-galactosidase A enzyme deficiency, leading to the progressive accumulation of glycosphingolipid globotriaosylceramide (Gb3) in the lysosomes of the nervous, cardiac and renal systems and in the skin and the eyes.1-9

Main ophthalmological findings include cornea verticillata, anterior and posterior subcapsular cataracts (the latter is known as Fabry cataract) and conjunctival and retinal vascular tortuosity. However, other less common manifestations, such as uveitis, central retinal artery occlusion, nystagmus, papilledema, optic atrophy or periorbital edema, may occur.1-4

The following clinical case of a symptomatic female carrier raises several questions regarding the role of the ophthalmologist, both in the early diagnosis and in the monitoring of FD patients who are candidates for enzyme replacement therapy (ERT).

CASE REPORT


Family history was negative for heart disease or FD. She did not have any other significant personal systemic or ophthalmological history. The clinical findings associated with the patient's disease were predominantly septal hypertrophic cardiomyopathy with severe left ventricular dysfunction, chronic renal failure and cutaneous angiokeratomas.

Visual acuity was 20/40 (with stenopeic pinhole [WSP]: 20/25 difficult) in the right eye and 20/50 (WSP: 20/30 difficult) in the left eye. Pupil reflexes and extrinsic ocular motility were within normal limits.

Mild conjunctival hyperemia without vascular tortuosity was observed on biomicroscopy. Of particular interest was the presence of corneal epithelial
opacity with whitish whorl-like lines converging in the lower central region of both eyes in a symmetrical fashion (Figures 1 and 2), by which the presence of cornea verticillata was confirmed. Moreover, incipient moderate nuclear and subcapsular cataracts were observed in both eyes. In the ocular fundus, the posterior pole showed a normal appearance with no vascular changes or other retinal lesions.

These ophthalmological findings corroborated the diagnosis of late-onset FD in a heterozygous female with no other known family history.

Figure 1. Image of cornea verticillata in the patient’s right eye. Epithelial opacity affecting the lower central region, formed by white whorl-like lines producing a radiating pattern as they go from the center to the corneal periphery can be observed with the slit lamp. As is typical in this disease, the involvement is bilateral and symmetrical and does not produce visual changes.

**DISCUSSION**

Cornea verticillata is a rare alteration observed in Fabry disease, Tangier disease, striate melanokeratosis, Melkerson-Rosenthal syndrome and as a side effect of certain drugs (such as amiodarone, quinacrine, chloroquine, indomethacin and chlorpromazine). Among these etiologies, this type of corneal opacity has been seen to occur most frequently in FD and in association with the use of amiodarone. In the majority of patients with FD, opacities are generally brown-colored with fine horizontal lines curving in a radial pattern from a point below the center toward the periphery of the cornea, in both eyes. However, in some cases it is limited to a central location and can, more rarely, take on a grayish or whitish tone, as was the case in our patient (Figure 2). Despite these changes, cornea verticillata does not usually cause visual defects.

The corneal opacity which appears with the chronic use of amiodarone is slightly different and characterized by horizontal lines with some arborization at their extremities, giving the typical “cats’ whiskers” appearance. Accordingly, the differential diagnosis in the case of a chance observation of cornea verticillata in a routine ophthalmological examination is very narrow, the only diagnostic tools required being an accurate clinical history and a slit lamp.

In Fabry disease, cornea verticillata is a highly characteristic early finding consistently observed both in male patients and in female carriers, thus emphasizing the relevance of the ophthalmological evaluation in the early detection of disease and in the family study of female carriers. The time between suspected diagnosis and confirmation by genetic and biochemical tests could be reduced by this evaluation and ERT could be implemented more rapidly. In this way, potential complications of this disease could be avoided and the associated morbidity and mortality reduced, given the availability of an effective and safe treatment.

No statistically significant relationship has been established between cornea verticillata and the progression of FD or the degree of systemic involvement, so this will not add any information on severity to the diagnosis and no predictive value regarding the progress of the disease will be obtained.

Finally, some evidence of a lower prevalence of cornea verticillata has been observed in some series of patients who had been receiving ERT for more than three months, suggesting a possible treatment effect. This may suggest a possible role for cornea verticillata as an indicator of treatment response. However, more research is required in this area due to the difficulty and subjectivity involved in monitoring progress with the slit lamp and currently available photographic techniques.

In short, given its high sensitivity and specificity, cornea verticillata can be considered as an ophthalmological marker for Fabry disease. For this reason, we encourage general ophthalmologists, and those who are not familiar with this finding, to find out more about recognizing this condition and about its clinical implications, with the aim of increasing the number of early diagnoses of patients with Fabry disease.
REFERENCES


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Figure 2. Images of cornea verticillata at greater magnification.
In this image, the glycosphingolipid deposits forming the characteristic epithelial opacity can be observed on biomicroscopy. The fine whitish lines do not have arborizations at their extremities, which distinguishes them from the so-called “cats’ whiskers” caused by amiodarone deposits.