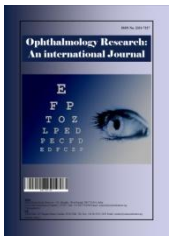

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The Importance of Molecular Testing for the Diagnosis of Fabry Disease Manifested by Cornea Verticillata Only

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Authors' contributions

This work was carried out in collaboration among all authors. Authors ACH and TSM designed the study, wrote the first draft of the manuscript and managed the literature search. Authors TCR and DAC revised it critically for intellectual contents. Authors ACH, TSM and VR were involved in the assessment and treatment of the patient. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aims: To describe a Fabry disease, that it's diagnosis was only possible through the molecular test
Presentation of Case: L.A.P. female, 42 years old, lawyer, seen by the ophthalmology department for routine consultation only with refractive complaints. Fundus of the eye: Mild narrowing with increased vascular brightness and presence of pathological arteriovenous crossings. The rest of the exam was within normal limits.
Therefore, a genetic test with the dosage of the α-Gal enzyme was requested, which evidenced the alteration in it, confirming the diagnosis of Fabry disease.
Discussion: A Fabry Disease (FD) is an inborn error of glycosphingolipid (GL) metabolism, resulting from deficient activity of the enzyme alpha-galactosidase A (α -Gal). It has X-chromosome-linked inheritance, affecting mainly males, with an estimated prevalence of 1:40,000 males. The

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expression of the disease in heterozygous female patients can vary from an asymptomatic condition to a severe systemic disease, like that which occurs in men.
Conclusions: The ophthalmological examination played an important role in the diagnosis, as this change is highly suggestive of the disease, in order to avoid erroneous and late diagnoses that can cause consequences for patients with this condition.

Keywords: Fabry disease; genetic error; verticillate cornea.

1. INTRODUCTION

[A Fabry Disease (FD) is an inborn error of glycosphingolipid (GL) metabolism, resulting from deficient activity of the enzyme alpha-galactosidase A (α -Gal). It has X-chromosome-linked inheritance, affecting mainly males, with an estimated prevalence of 1:40,000 males[1,2,3]. The expression of the disease in heterozygous female patients can vary from an asymptomatic condition to a severe systemic disease , like that which occurs in men[2-4].

Due to the deficiency in the activity of this enzyme, there is a progressive accumulation of GL in several organs, which may affect the cardiac, renal, cutaneous, nervous, gastrointestinal tract and eyes systems[3-5].

Diagnosis is difficult when the family history is negative for the disease. In affected men, the definitive diagnosis is made by determining the activity of the α-Gal enzyme, which can be measured in plasma, leukocytes and fibroblasts. α-Gal activity in most affected men is less than 3% of normal[4-6]. In heterozygous women, it is common to see enzyme activity dosage results within reference values. Clinical screening of women with the disease can be performed by finding the cornea verticillata (VC) [2,3,5,6].

Ophthalmological findings have become one of the disease markers, which are essential to aid in diagnosis. Conjunctival changes such as vascular dilation and tortuosity, caliber irregularity and aneurysm formation may be present. Retinal alterations compatible with findings of hypertensive retinopathy secondary to the presence of renal pathology and arterial hypertension can be diagnosed. [4,6,7,8].

VC is characterized by the presence of yellowish corneal opacities in one or more lines radiating from a point near the center of the cornea towards the periphery. This is the most common ocular finding and is present in almost all heterozygous males with the disease and in approximately 70 to 90% of heterozygous females. There is no report of impairment of visual acuity and no correlation with disease severity has been established[5,6,7.9].

VC is also associated with the use of some drugs, such as amiodarone phenothiazine, chlorfazimine, chloroquine and indomethacin. In the case of DF, this change does not disappear with treatment, unlike what occurs in cases associated with the chronic use of medication[6,9,10].

The ophthalmologic exam is an important tool in the diagnosis of carriers, since the dosage of a-Gal enzyme activity is not always reduced in these women and the molecular exam is difficult to access. [4,6,9].

2. CASE REPORT

L.A.P. female, 42 years old, lawyer, seen by the ophthalmology department for routine consultation only with refractive complaints. Denied previous systemic pathologies, as well as chronic use of any systemic and topical medications. Denied personal and family history of ophthalmologic comorbidities.

Best corrected visual acuity: 20/20 in both eyes (AO).

Intraocular pressure: 12/14mmHg (11:00 am)

Biomicroscopy: Dilated and tortuous episcleral and conjunctival vessels in AO. Vertical cornea AO. No more changes. (Figs 1 and 2).

Fundus of the eye: Mild narrowing with increased vascular brightness and presence of pathological arteriovenous crossings. The rest of the exam was within normal limits.

Therefore, a genetic test with the dosage of the α-Gal enzyme was requested, which evidenced the alteration in it, confirming the diagnosis of FD. (Fig. 3).

Prescribed the refraction for better visual acuity of the patient and referred to a specialist in Internal Medicine for monitoring of the systemic condition.

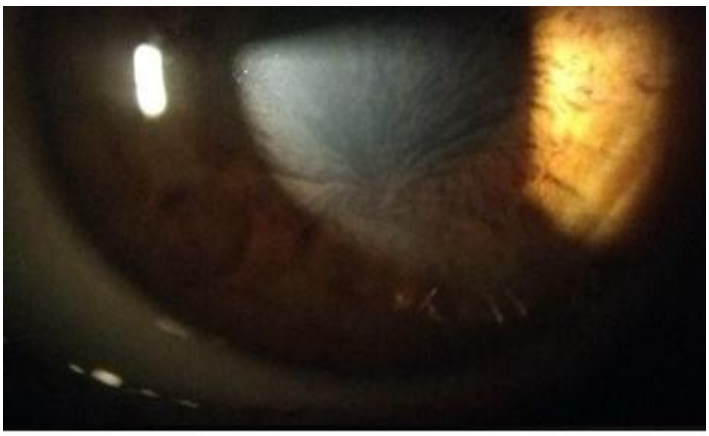

Fig. 1. Cornea verticillata

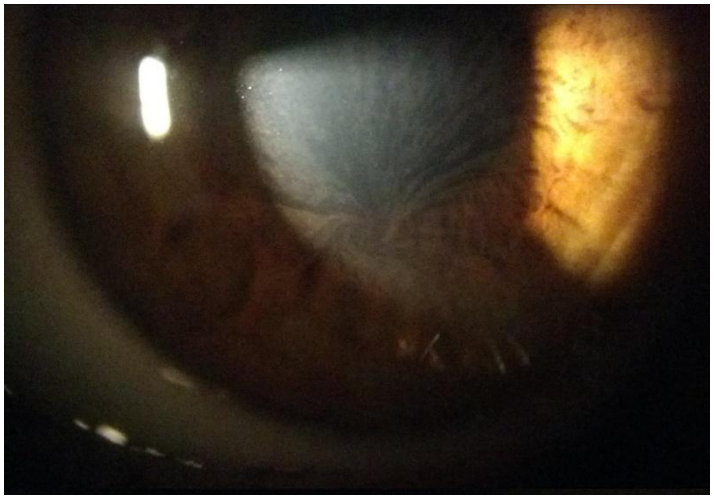

Fig. 2. Córnea verticillata

Request for Fabry disease testing (inheritance: X-linked)

Clinical information: no clinical information.

Results:

Gene sequencing	GLA	- heterozygous mutation (c.679C>T p.R227X)
HPLC/Tandem MS	lyso-Gb3	- 6,7 ng/ml (reference: 1,3 ± 0,9 ng/ml; 95% percentile: 3,2 ng/ml)

GLA (Fabry disease, OMIM 301500)

Inheritance: X-linked

Reference sequence: NM_000169.2

Location	Nuc. Change	AA change	Ref.	Evaluation
Ex05	c.679C>T (het)	p.R227X	Davies, 1993	disease-causing

Fig. 3. Molecular test showing the mutation in the alpha-galactosidase gene

3. DISCUSSION

The classic form of FD usually occurs in men. Symptoms appear in childhood and adolescence, with acroparesthesia, angiokeratomas, cornea verticillata and hypohidrosis. Usually around the third to fifth decades of life, there is an increase in symptoms, with progressive impairment of the cardiac, renal and cerebral systems[5,11,12,13]. Cardiovascular findings include arterial hypertension, left ventricular hypertrophy and myocardial ischemia. Kidney disease can culminate in chronic kidney failure[11,14,15].

In general, female patients are asymptomatic or exhibit mild manifestations. Even in women with no symptoms of the disease, VC can be observed on the ophthalmological examination[13-16]. The patient in the present report was asymptomatic both from a systemic and ophthalmological point of view, which corroborates what is found in the literature.

Late diagnosis has significant clinical implications for the patient, as FD can lead to end-stage renal disease and life-threatening cardiovascular or cerebrovascular complications[12,14,17,18]. These alterations are not yet present in the patient in the present report, and she is totally asymptomatic at diagnosis.

This type of ocular change can also occur if some drugs are used, such as amiodarone, phenothiazine, chloroquine, indomethacin and chlorfazimine[4,11,12,14,16]. These medications were not used by the patient. Given the absence of previous known systemic comorbidities and the use of drugs that could cause VC, it was decided to carry out the molecular genetic test for DF, since it is an underdiagnosed disease, since its diagnosis is performed through genetic tests that are often difficult to access to the population.

Diagnosis is difficult when the family history is negative, since most patients do not present symptoms from an ophthalmological point of view, which can delay the elucidation of the condition[12,17,18,19]. The patient did not have relatives with relevant ophthalmological and systemic conditions, which reinforced the need for genetic testing to elucidate the diagnosis, as the family history is negative for FD and other pathologies.

Therefore, if VC is observed in the slit-lamp examination, clinical suspicion of FD should be considered and immediate referral for a full investigation is imperative. Therefore, the ophthalmologist must be aware of the importance of recognizing VC and its clinical repercussions[4,11,16-19]. Therefore, the ophthalmologist must be aware of the importance of recognizing VC and its clinical repercussions, as performed in this report, in order to use all available complementary methods to make the correct diagnosis and treatment of these patients.

4. CONCLUSION

DF is an inborn error of glycosphingolipid metabolism, resulting in a deficiency of the enzyme alpha-galactosidase (α-Gal).

Heterozygous women are asymptomatic or show mild manifestations, and the cornea verticillata is one of the suspected forms of diagnosis.

This condition can be manifested by dilation, tortuosity, and conjunctival and episcleral vascular aneurysms, deposition of granular material in the lens, and anterior subcapsular cataract. Retinal alterations exacerbated by the presence of kidney disease and arterial hypertension can be found.

Systemically, with the progressive impairment of the vascular system, cardiac, renal and cerebral alterations can lead the patient to death.

The definitive diagnosis is made by determining the activity of the α-Gal enzyme and by mutation in the GLA gene.

VC was observed in 70 to 90% of the cases of FD, also being associated with the use of certain drugs, such as amiodarone, phenothiazine and chloroquine. Careful eye examination is important, as the dosage of α-Gal enzyme activity is not always decreased and molecular examination is not easily accessible.

The ophthalmological examination played an important role in the diagnosis, as this change is highly suggestive of the disease, in order to avoid erroneous and late diagnoses that can cause consequences for patients with this condition.

CONSENT

All authors declare that ‘written informed consent was obtained from the patient (or other approved

parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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