Characterization of ocular involvement in patients with Fabry disease

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Research

Keywords: Fabry disease, corneal verticillata, retinal vessel tortuosity, optical coherence topography

Posted Date: March 12th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-16983/v1>

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Abstract

Background Fabry diseases (FD) is an X-linked recessive lysosomal storage disease that is caused by deficient activity of the lysosomal enzyme α -galactosidase A. Ocular abnormalities have been regarded as characteristic, frequent and easily accessed findings in Fabry disease, and have a high diagnostic value. Some of the ocular findings are easy to find using slit lamps. But some are only visible with the imaging devices such as in vivo confocal microscopy (IVCM) and optical coherence topography (OCT) are prone to be ignored. The aim of this study was to examine the prevalence and characteristics of ocular findings in patients with FD.

Result 32 FD patients diagnosed by gene test from one medical center were enrolled. Ocular examinations including slit-lamp examination, ophthalmological fundus imaging, in vivo confocal microscopy as well as optical coherence topography were performed. Among these patients, the prevalence of corneal verticillata was 96.8% (31/32). Corneal examination with in vivo confocal microscopy demonstrated hyper-reflective intracellular inclusions located within the basal epithelial cells. There were no obvious abnormalities in the Bowman's membrane, stroma or endothelium. Conjunctival vessel malformations were observed in 62.5% (20/32) of patients and retinal vessel tortuosity was observed in 68.7% (22/32) of patients. Optical coherence topography showed many strong hyper-reflective foci in the inner retinal layer, in 62.5% (20/32) patients; the foci may be the images of retinal vascular plexi. Spoke-like opacity of lens was only in two patients. An old retinal artery occlusion was observed in one other patient.

Conclusions Corneal verticillata, hyper-reflective foci on OCT, retinal vessel tortuosity and conjunctival vessel malformation show a high prevalence in FD. Epithelium deposition and small vessel malformation may be two basic types of all of these ocular involvements. And these ocular manifestations are characteristic and easily accessible, and should be considered diagnostic criteria for Fabry disease.

Background

Fabry disease (FD) is an X-linked recessive lysosomal storage disease that is caused by deficient activity of the lysosomal enzyme α -galactosidase A. This deficiency results in progressive lysosomal accumulation of glycosphingolipids with α -galactosyl residues, particularly globotriaosylceramide (Gb3), which accumulates in epithelial cells of different organs. The accumulation in kidney, heart and nervous system lead to progressive kidney failure, cardiomyopathy and Fabry-associated pain or stroke, which contribute significant morbidity and mortality. FD is a rare disease, and the diagnosis is often missed or delayed because the early symptoms are subtle or non-specific.[1][2]

Some of the distinctive features of FD are ocular manifestations, of which corneal verticillata, also known as vortex keratopathy, is the most commonly reported. Tortuous conjunctival and retinal vessels and spoke-like lens opacities are also exhibited in a number of patients and usually referred as Fabry-related ocular lesions.[3][4] Most Fabry-related ocular lesions do not affect vision, but they are often an early and unique sign of this disease and can be detected in a routine, non-contacting eye exam.[5] In this report, we describe the features of common ocular manifestations of FD, not only those detected by slit-lamp examination, but also those revealed by ocular imaging devices. Some of the manifestations we found differ somewhat from those reported in earlier studies, and we hope that the novel ocular characteristics may aid in the prompt and accurate diagnosis of FD.

Methods

Subjects

At our hospital, a total of 40 patients with FD of were included in this study between January, 2014, and December, 2018. All patients had their diagnosis confirmed by the presence of a α -galactosidase A mutation. Informed consent was obtained from all participants, and the study was approved by the Institutional Review Board of Peking University First Hospital and followed the tenets of the Declaration of Helsinki.

Clinical examination

Medical history was taken of all patients before a complete ophthalmologic examination. A complete ophthalmologic examination, including visual acuity, intra-ocular pressure, anterior segment slit-lamp examination, color fundus photography and optical coherence tomography (OCT) were performed on all patients. Intra-ocular pressure was measured with a non-contact tonometer (CT800, Topcon, Tokyo, Japan). Undilated digital fundus photographs were taken using a 45-degree digital retinal camera (CR-2, Canon, Tokyo, Japan). A retinal image of each eye was obtained, with images centered at the fovea. The branching vessels within the macular lutea region were evaluated.

OCT examination

All patients underwent high definition OCT (Spectralis, Heidelberg Engineering, Germany) scanning of the macular area without pupil dilation. A trained technician blinded to the study group performed the scans after the ophthalmological examination. A one-line 6-mm horizontal scan was made with a high definition protocol focused on the fovea. Hyper-reflective foci were defined as discrete and well-circumscribed dots of higher reflectivity compared with outer nuclear layer(ONL)or retinal nerve fiber layer (RNFL).

Corneal confocal microscopy examination

As a further, but cornea-contacting examination, in vivo corneal confocal microscopy (IVCM) was recommended to all of the patients, but only one-third of them agreed to such an examination Those patients underwent IVCM (Heidelberg Tomography 3, Heidelberg Engineering, Germany) examination under topical anesthesia. The eyes were anesthetized by instilling 4% Oxybuprocaine Hydrochloride (Santen Pharmaceutical Co.,Ltd) in the lower conjunctival cul-de-sac. The patient was positioned in front of the microscope with their chin placed in the chin rest and their forehead placed up against the forehead support. A sterile single-use contact element (TomoCap) was placed between the microscope and the cornea. The confocal image plane inside the cornea was moved manually at the microscope lens. Images of the corneal layers were taken from the central cornea. The IVCM provides images measuring 400 *400 μ m. The images were recorded digitally and stored on the system's hard in order to select pictures of the best quality and analyze corneal morphology.

Results

The subject group included 30 males and 10 females with a mean age of 31.6 ± 16.4 years (range, 9–60 years) and normal IOP (14.25 ± 3.15 mmHg).

Corneal verticillata, the most common and distinctive finding visible bilaterally by slit-lamp microscopy, were present in nearly all of the patients (38 patients, 95%) (Fig. 1A). Only one patient did not have an obvious corneal verticillata, but some brown lines were present on that patient's corneas. In eyes examined with IVCM, hyper-reflective cells were noted across the whole epithelial layer at the location of the corneal verticillata (Fig. 2). However, the Bowman's, stromal and endothelial layers appeared normal on IVCM. Two types of conjunctival vascular abnormalities were found in this group of patients. One type was vascular tortuosity, which was often seen on the nasal and temporal bulbar conjunctiva, but which is also seen in other diseases. The second type was vessel aneurysmal dilatation, which was often seen in the nasal-inferior quadrant of the bulbar conjunctiva. This vessel malformation with dilatation and occlusion was more distinctive than the first type of vascular abnormality, and was seen in 30 patients (75%) (Fig. 1C). It was noted that more than one aneurysmal dilatation could be found on the conjunctiva of some patients (Fig. 1D). Fabry-related lens opacity is very characteristic but rare. Only two of our patients had such a bilateral classical spoke-like appearance on the capsule of their lens (Fig. 1B).

Retinal vascular tortuosity was also a common finding, present in 32 patients bilaterally (80%). It was more obvious on venules than arterioles. Most of the patients (22 cases, 55%) had tortuosity on both primary and secondary branch vessels (Fig. 3A), whereas some patients (10 cases, 25%) had tortuosity only on the secondary branch vessels (Fig. 3B). OCT imaging showed bilateral multiple distinct, hyper-reflective foci (HRF), with diameters of 10–30 μm , scattered in the retina, in the inner nuclear layer (INL), inner plexiform layer (IPL), ganglion cell layer (GCL) and nerve fiber layer (NFL) (Fig. 3C). Based on the intensity of reflection, such foci could be divided into two categories, strong HRF and weak HRF (near normal foci). The reflectivity of the strong HRF was similar to that of the retinal pigment epithelium band (Fig. 3D), whereas weak HRF had reflectivity similar to that of the IPL or NFL (Fig. 3F). In this group of 40 patients, 27 (67.5%) had strong HRF and 13 (32.5%) had weak HRF.

Among all of the patients, only one person had a history of sudden vision loss in his right eye, and he had been diagnosed many years before with central retinal artery occlusion. His OCT scan revealed a partial loss and thinning of the inner retinal layers (NFL/GCL/IPL/INL) of right eye. The outer retinal layers remained intact (Fig. 3E). Intact retinal layers with weak HRF were found in his left eye (Fig. 3F).

Discussion

FD is a rare disease with diverse signs. The ocular manifestation was first noticed and reviewed by Drs. Spaeth and Frost in 1965.[6] Since then, corneal verticillata, cataracts, and conjunctival and retinal vascular abnormalities have been considered the typical findings in FD.[6][7][5] The whorl-like corneal opacities were distinctive and reported frequently, but the prevalence varied from 53–100% in earlier papers.[3][8][9] In this group, whorl-like opacities of cornea could be seen in almost all patients. The prevalence of cornea verticillata in FD patients confirmed by enzymatic and genetic diagnosis was 95%. This variability may result from the selection bias or observer errors. By scanning with IVCM, we observed hyper-reflective intracellular inclusions from the superficial to basal corneal epithelium, under the corneal verticillata. It has also been reported that complex basal-Bowman's membrane irregularities can be found in FD patients, but we did not detect that type of abnormality.[10][11]

Vascular tortuosity of the conjunctiva and retina was thought to be a marked sign of FD. [12] A recent research revealed that vascular tortuosity of upper eyelid was also a feature of FD.[13] However, we found that vascular tortuosity was less specific, as that sign can also be found in many elderly people and in patients with other diseases. Conjunctival aneurysmal dilatation and retinal HRF were more-distinctive signs of FD. More than half of the patients had such an aneurysmal dilatation.

HRF in the retina were more common and were detected in all of the patients. We are not the first research group to have scanned FD patients with OCT. Albert et al.[3] reported normal macular appearance on OCT scanning in a group of 23 patients with FD. The HRF may have been overlooked in that study because they did not affect the figure of the retinal layers. To our knowledge, the present report is the first description of such foci and we suggest that they are a distinctive ocular feature of FD. The small foci spread from INL to NFL. Based on that spread, we think that the foci in the NFL and GCL may be the images of cells of the superficial vascular plexi, and that the foci in the INL and IPL may be the images of vascular-wall cells of deep vascular plexi. Although most of the patients have a strong HRF in retina, some ones have foci with a somewhat weak reflection. Actually, the weak HRF could also found on the retina of normal persons. More observations need to be taken to understand the difference of the two types of reflective foci.

Unique spoke-like lens opacities and retinal vessel obstructions were also found in the present group of patients, but they are not thought to be basic signs of FD because of the low prevalence.

Conclusions

Recently, enzyme-replacement treatment has become available for FD, heightening the importance of early diagnosis, so that treatment can be initiated before irreversible organ damage. The ocular findings from slit-lamp examination and imaging devices are distinctive, so vigilance by ophthalmologists and optometrists is increasingly valuable for early diagnosis of FD. Ophthalmologic evaluation is a suitable clinical screening tool for FD, potentially providing quick, early diagnosis and a potential substitute for pathological and/or gene analyses. We suggest that any patients with corneal verticillata, conjunctival vessel aneurysmal dilatation, retinal vessel tortuosity or hyper-reflective foci on OCT should undergo a thorough review of symptoms and family history to exclude the possibility of FD.

Abbreviations

OCT
optical coherence topography
IVCM
in vivo confocal microscopy
ONL
outer nuclear layer
INL
inner nuclear layer
IPL
inner plexiform layer

RNFL
retinal nerve fiber layer
GCC
ganglion cell complex

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Peking University First Hospital and followed the tenets of the Declaration of Helsinki.

Consent for publication

All presentations of case reports have consent to publish.

Availability and data and materials

All data supporting the results reported in this study are available from the corresponding author upon request.

Funding:

1 ULM-PUHSC joint institute for translational and clinical research (No: PKU2017ZC001-5)

2 The National Natural Science Foundation (China) (No:81100840)

Conflict of Interest Disclosure

All authors have completed and submitted the ICMJE Form Disclosure of Potential Conflicts of Interest and none were reported.

Author's contributions:

WY and ZW conceived and designed the study. YY and YXM helped us to diagnosed these patients. WY, YXY, SWJ and ZYW performed the observations and recorded the data. YW and ZW wrote the paper. YW, ZW reviewed and edited the manuscript. All authors read and approved the manuscript.

Acknowledgements

We thank staff at Liwen Bianji, Edanz Group China (www.liwenbianji.cn/ac), for critically reviewing a draft of this manuscript.

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Figures

Figure 1

External slitlamp photographs showing manifestations of anterior segment. A Cornea verticillata; B Spoke-like opacity of lens; C & D: Conjunctival vessel aneurysmal dilatations.

Figure 2

Images of in vivo corneal confocal microscopy of corneal epithelium at different depth. A At the depth of 10 μm ; B At the depth of 30 μm ; C At the depth of 40 μm ; D At the interface of epithelium and Bowman's layer.

Figure 3

Images showing manifestation of posterior segment. A & B: Color fundus photograph showing retinal vascular tortuosity; C & D: Images of OCT showing retinal hyper-reflective foci; E & F: Retinal OCT image of bilateral eyes of the patient with vision loss