Open Journal of Clinical & Medical Images

www.jclinmedimages.org

Case Report

Open Access, Volume 3

Change in tear film parameters in a patient with Fabry disease undergoing enzyme replacement treatment (ERT): Case report

Mario Troisi[1]; Salvatore Troisi[2]*; Ciro Costagliola[1]

[1]Eye Clinic, Department of Neurosciences, Reproductive and Dentistry Sciences, University of Naples Federico II, Naples, Italy.

[2]Ophthalmologic Unit, Head-Neck Department, Salerno Hospital University, Italy.

***Corresponding Author: Salvatore Troisi**

Ophthalmologic Unit, Head-Neck Department, Salerno Hospital, University, Italy.

Email: Salvatore.troisi @gmail.com

Received: May 16, 2023

Accepted: Jul 03, 2023

Published: Jul 10, 2023

Archived: www.jclinmedimages.org

Keywords: Ocular manifestations of fabry disease; Dry eye disease; Ocular surface disease; Cornea verticillata; Alpha-galactosidase a enzyme replacement therapy.

Abstract

Fabry disease is a rare X-linked lysosomal storage disease caused by an inherited defect of alpha-galactosidase a enzyme, resulting in progressive renal failure, cardiovascular and cerebrovascular changes. The most frequent ocular manifestations are typical opacities of the cornea and lens and tortuosity of the conjunctival and retinal veins. ERT is a specific treatment that can provide clinical benefits on different outcomes and organ systems damaged by glycosphingolipid deposition.

The authors describe a case of Fabry disease affected by dry eye; six months after the start of ERT they noticed a marked improvement in lacrimal parameters, in the absence of any ophthalmologic therapy. This finding suggests an effect of ERT on precorneal tear film alterations. Therefore, they believe that prospective studies are needed to confirm this link and to clarify its possible mechanisms.

Introduction

Fabry disease is a rare, underdiagnosed, X-linked genetic lysosomal storage disease, secondary to alpha-galactosidase A enzyme deficiency, leading to sphingolipids building up in the walls of blood vessels and other organs [1]. Progressive renal failure is a major source of morbidity; additional complications result from cardio- and cerebrovascular involvement. Diagnosis is easy in males, with dosage of alpha-galactosidase A enzyme activity into leukocytes, but more difficult in females who can express normal residual activity [2]. Early recognition of Fabry disease is important because treatments are available, but it may be challenging. Enzyme replacement therapy (ERT) with recombinant human alpha-galactosidase has been used for the treatment of Fabry disease since 2001 in Europe and 2003 in the USA. Trials comparing enzyme replacement therapy to placebo show significant improvement with enzyme replacement therapy in regard to microvascular endothelial deposits of globotriaosylceramide and in pain-related quality of life [3,4]. Survival is reduced in affected males and symptomatic female carriers [3].

Ophthalmological manifestations are common in Fabry disease and result from the progressive glycosphingolipids deposition in various ocular structures [5]. Typical ocular manifestations, identifiable during a routine eye examination, are: cornea verticillata, spoke-like cataract, conjunctival and retinal vessel tortuosity [6,7]. Since the eye is an organ easily investigated with minimally invasive technologies, ocular manifestations can be useful for monitoring the natural history of Fabry disease and response to ERT.

The authors describe a case of Fabry disease affected by typical ocular manifestations and dry eye and discuss a possible effect of ERT on precorneal tear film alterations.

Clinical case presentation

A 50-year-old male patient from Maghreb was evaluated for foreign body sensation. The initial evaluation was made by visual acuity assessment and slit-lamp examination. The evidence of cornea verticillata, in a patient never treated with amiodarone, lead to suspect Fabry disease.

The patient underwent a complete ophthalmologic evaluation and clinical examination for dry eye; symptoms of discomfort (OSDI score), tear film (Schirmer I test, TFBUT) and ocular surface damage (corneal fuotest) were investigated.

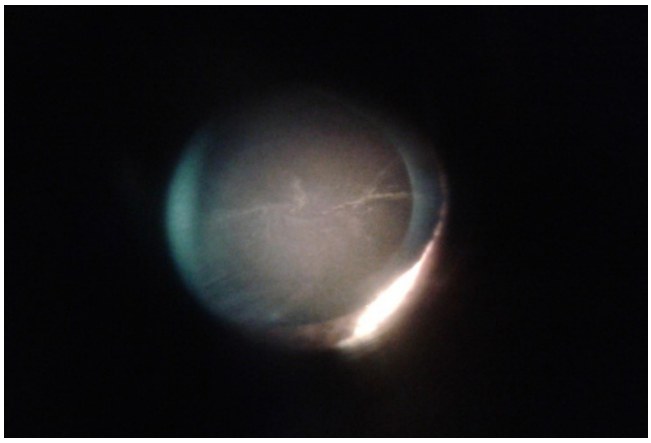

Figure 1: Cornea verticillata at slit lamp examination.

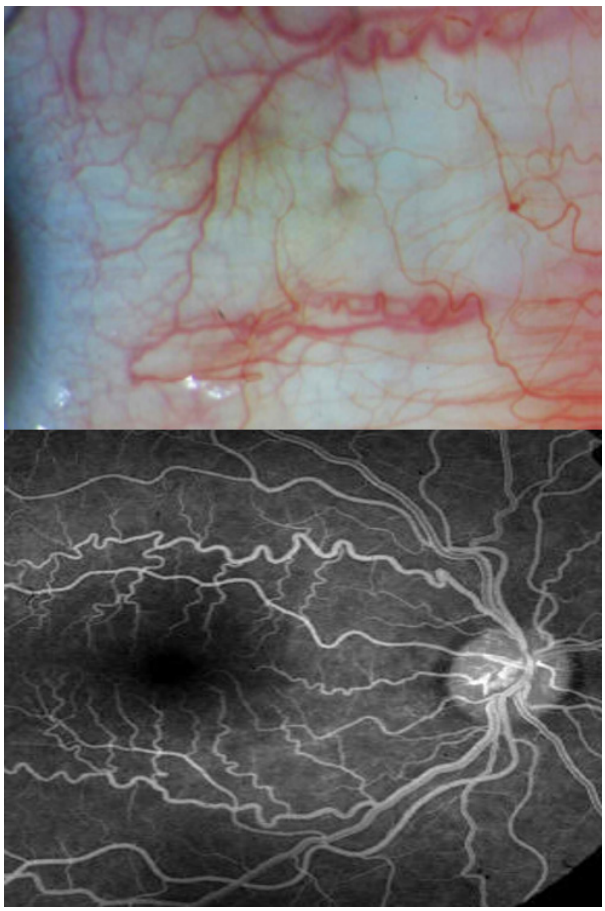

Figure 2: Conjunctival and retinal vessels tortuosity.

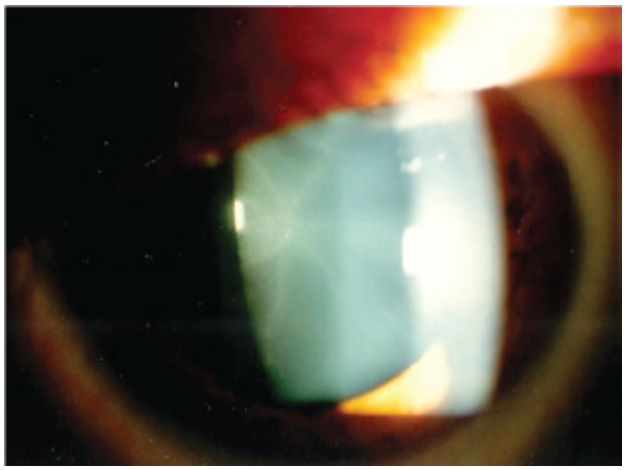

Figure 3: Lens opacities with cortical spokes in Fabry disease.

Bilateral whorl-like opacities located in the superficial corneal layers (Figure 1), conjunctival and retinal vessel tortuosity (Figure 2) and asymmetrical spoke-like cataract (Figure 3) were recorded in this patient. The OSDI score (34); Schirmer test 1 (RE: 6 mm and LE 5 mm), and TFBUT (3 sec in OU) were abnormal. Corneal (4) and conjunctival (6) NEI scores were impaired. No signs of infections or ocular allergy. BCDVA: RE: 20/25 (sph +0,5=cyl +0,75 ax 170°); LE:20/25 (sph +0,25=cyl + 0,75 ax 180°).

The patient also underwent cardiac, neurological, dermatological and renal evaluations and laboratory tests. TTE exam identified hallmarks of Fabry's disease cardiomyopathy. Susceptibility-weighted T2* studies demonstrated a low-signal-intensity abnormality in the diencephalic area, whereas CT demonstrated the pulvinar to be mineralized. Kidney function was normal. No angiokeratomas were present. The alpha-galactosidase activity level was zero. Typical mutations in the GLA gene were detected.

The patient underwent ERT and was monitored by internists. The prescribed ophthalmological treatment was hyaluronic acid-based eye drops three times a day and a night-time lubricating gel.

At ophthalmological check-up carried out six months later, the corneal and crystalline opacities were substantially unchanged, as the vessel tortuosities. Visual acuity was also unchanged. The patient reported a significant improvement in dry eye symptoms, despite not having undergone treatment with tear substitutes, both due to the cost of the eye drops and because he was more focused on the other manifestations of the disease.

Evaluation of ocular surface and tear parameters: improvement of OSDI (score: 11) and TFBUT (RE: 8 sec; LE: 9 sec); Schirmer test 1 (RE: 8 mm; LE: 7 mm); Corneal Fluotest negative in both eyes.

Discussion

Cataracts, tortuous vessels and corneal opacities usually do not cause significant visual impairment or other ocular symptoms, but are important markers of the disease, with diagnostic and prognostic implications [6]. Cornea verticillata has been the most frequently reported ophthalmic abnormality in both hemizygous males and heterozygous females and may repre-

sent a useful diagnostic marker. Tortuous vessels and cataract were more frequent in males than in females [8]. Tortuosity of the conjunctival and retinal vessels has been associated with more rapid disease progression and more severe systemic involvement [8,9].

In the case under examination, the presence of dry eye according to the TFOS DEWS II 2017 criteria was detected at the first observation, in the absence of signs of infection or allergy. The improvement in ocular surface parameters and symptoms (OSDI score) in the absence of any local therapy was attributed to systemic enzyme replacement treatment performed for six months.

Dry eye finding in Fabry patients has been reported in few works in literature, sometimes in association with altered pupillary motility (reduced constriction with pilocarpine), suggesting that there is an impairment of autonomic function [10,11]. In a clinical study of 31 patients, 11 patients (35%) were diagnosed with dry eye; it was also found that patients treated with ERT seemed to have a lower risk of developing dry eye ($p>0.1$) [12].

Alterations of tear film and ocular surface have therefore already been correlated to Fabry disease, but the precise mechanisms underlying this relationship are not known; furthermore, any effects on the lacrimal parameters of ERT have not been studied [12-14]. The data relating to the presented clinical case are very suggestive of a possible role of ERT on the improvement of tear film dysfunction. We therefore believe that this probable association needs to be investigated through prospective studies.

Conclusions

Cornea verticillata and spoke-like cataract are ocular manifestations identifiable during a routine eye examination in Fabry patients. They are the most characteristic ophthalmological manifestations of ophthalmic abnormality in both males and females. Tortuous conjunctival and retinal vessels and Fabry cataracts were more frequently found in males than in females. ERT is a disease-specific treatment for patients with Fabry disease that may provide clinical benefits on several outcomes and organ systems [15].

In this case, at the first visit, in addition to the most typical signs of Fabry disease (cataract, corneal opacities and tortuous vessels), a subjective and objective picture of dry eyes was observed, significantly improved after six months of ERT and in the absence of any ophthalmological treatment. Specific prospective studies are needed to confirm any positive effect of enzyme replacement therapy on tear and ocular surface parameters and to understand the possible mechanisms underlying this relationship.

Abbreviations: ERT: Enzyme Replacement Therapy; RE: Right Eye; LE: Left Eye; OU: Oculus Uterque; OSDI Score: Ocular Surface Disease Index; TFBUT: Tear Film Break-Up Time; BCDVA: Best Corrected Distance Visual Acuity; Sph: Sphere (In Diopters); Cyl: Cylinder (In Diopters); Ax: Axis; TTE: Transthoracic Echocardiogram; CT: Computed Tomography.

References

1. Germain DP. Maladie de Fabry (déficit en α-galactosidase A): physiopathologie, signes cliniques et aspects génétiques [Fabry's disease (α-galactosidase-A deficiency): physiopathology, clinical signs, and genetic aspects] J Soc Biol. 2002; 196:161–173
2. Michaud M, Mauhin W, Belmatoug N, Bedreddine N, Garnotel R, Catros F, Lidove O, Gaches F. Maladie de Fabry : quand y penser ? [Fabry disease: A review]. Rev Med Interne. 2021 Feb; 42(2):110-119.
3. El Dib R, Gomaa H, Carvalho RP, Camargo SE, Bazan R, Barretti P, Barreto FC. Enzyme replacement therapy for Syst Rev. 2016 Jul 25; 7(7): Anderson-Fabry disease. Cochrane Database CD006663.
4. Hughes DA, Bichet DG, Giugliani R, et al. Long-term multisystemic efficacy of migalastat on Fabry-associated clinical events, including renal, cardiac and cerebrovascular outcomes. Journal of Medical Genetics. 2022 Dec 21:jmedgenet-2022-108669.
5. Mehta A, Ricci R, Widmer U, Dehout F, Garcia de Lorenzo A, Kampmann C. et al. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. Eur J Clin Invest. 2004; 34:236–242.
6. Orssaud C, Dufier J, Germain D. Ocular manifestations in Fabry disease: a survey of 32 hemizygous male patients. Ophthalmic Genet. 2003; 24:129–139.
7. Wiest MRJ, Toro MD, Nowak A, Baur J, Fasler K, Hamann T, Al-Sheikh M, Zweifel SA. Globotrioasylsphingosine Levels and Optical Coherence Tomography Angiography in Fabry Disease Patients. Journal of Clinical Medicine. 2021; 10(5):1093
8. Sivley MD, Wallace EL, Warnock DG, et al. Conjunctival lymphangiectasia associated with classic Fabry disease. British Journal of Ophthalmology 2018; 102:54-58.
9. Hauser AC, Lorenz M, Voigtlander T, Fodinger M, Sunder-Plassmann G. Results of an ophthalmologic screening programme for identification of cases with Anderson–Fabry disease. Ophthalmologica. 2004;218:207–9.
10. Nguyen TT, Gin T, Nicholls K, Low M, Galanos J, Crawford A. Ophthalmological manifestations of Fabry disease: a survey of patients at the Royal Melbourne Fabry Disease Treatment Centre. Clin Experiment Ophthalmol. 2005; 33:164–168.
11. Klein P. Ocular manifestations of Fabry's disease. J Am Optom Assoc. 1986; 57:672–674.
12. Cable WJ, Kolodny EH, Adams RD. Fabry disease: impaired autonomic function. Neurology. 1982; 32:498–502.
13. Fariselli C, Fresina M, Versura P, C Campos EC; Ocular surface impairment in Fabry disease. Invest. Ophthalmol. view Sci. 2019; 60(9):4713.
14. Troisi S, Turco V, Tenuta M, Rocco C, Cirillo SA. The first report of Fabry disease in Salerno province: diagnostic role and evolution of the ocular manifestations. Abstract book, International XIII Congress SICSSO 2014.
15. Arends M, Biegstraaten M, Wanner C, et al. Agalsidase alfa versus agalsidase beta for the treatment of Fabry disease: an international cohort studyJournal of Medical Genetics 2018; 55: 351-358.