# Conjunctival lymphangiectasia associated with classic Fabry disease

Melanie D Sivley,[1] Eric L Wallace,[2] David G Warnock,[2] William J Benjamin[1]

[1]Department of Optometry and Vision Science, University of Alabama at Birmingham, Birmingham, Alabama, USA
[2]Department of Medicine, Division of Nephrology, University of Alabama at Birmingham, Birmingham, Alabama, USA

**Correspondence to**
Dr Melanie D Sivley, Department of Optometry and Vision Science, University of Alabama at Birmingham, HPB Room 444 Birmingham, Alabama 35294-0010, USA; msivley@uab.edu

Received 26 December 2016
Revised 16 March 2017
Accepted 25 March 2017
Published Online First 12 May 2017

## ABSTRACT

**Background** Fabry disease (FD) is a treatable multisystem disease caused by a defect in the alpha-galactosidase gene. Ocular signs of FD, including corneal verticillata, are among the earliest diagnostic findings. Conjunctival lymphangiectasia (CL) has not previously been associated with FD.

**Methods** We examined the eyes of a cohort of 13 adult patients, eight men and five women, with documented classic FD, all treated with enzyme replacement therapy (ERT) at the University of Alabama at Birmingham between February 2014 and April 2015. The average age was 48 years with a range of 35–55 years for men and 21–71 years for women. The mean duration of ERT was 8.4 years (men 8.9 years, women 7.6 years) with a range of 4–14 years. Classical Fabry mutations included Q283X, R227X, W236X and W277X. A high resolution Haag-Streit BQ-900 slit lamp with EyeCap imaging system was used to record conjunctival images.

**Results** CL was observed in 11 of the 13 patients (85%) despite long-term ERT. Clinical presentations included single cysts, beaded dilatations and areas of conjunctival oedema. Lesions were located within 6 mm of the corneal limbus. Ten of the 13 subjects (77%) had Fabry-related cataracts and all 13 demonstrated bilateral corneal verticillata. Twelve of the 13 patients had evidence of dry eye, 9 of whom were symptomatic, and 10 had peripheral lymphoedema.

**Conclusion** CL represents a common but under-recognised ocular manifestation of FD, which persists despite ERT, and is often accompanied by peripheral lymphoedema and dry eye syndrome.

## INTRODUCTION

Fabry disease (FD) is a rare X-linked lysosomal storage disorder caused by a mutation in the gene coding for the enzyme alpha-galactosidase A that leads to limited or defective enzyme activity.[1] Consequently, globotriaosylceramide (Gb-3) progressively accumulates in lysosomes throughout the body. Patients with the classic form of FD present in childhood with acroparesthesias, hypohidrosis, angiokeratomas, ocular findings and gastrointestinal symptoms.[2 3] Ultimately, kidney failure, cardiomyopathy and arrhythmias, and cerebrovascular disease develop as Gb-3 builds up in vital organs and vascular endothelium causing widespread ischaemia and premature organ failure.[4]

Ocular signs are among the earliest clinical findings of FD, the most common of which is corneal verticillata, found in 95% of hemizygous men and nearly 90% of heterozygous women with classic mutations.[5–7] Other well-described ocular findings include tortuous conjunctival and retinal vessels, anterior 'propeller' and posterior sutural 'Fabry' cataracts.[5–7] Ocular findings have been associated with eye dryness, visual disturbances and eye fatigue,[8] but have not yet been shown to impact the overall quality of life for patients with FD.[9 10]

Conjunctival lymphangiectasia (CL) is a rare condition in the general population that accounts for 1% or less of all conjunctival lesions.[11–14] Having assessed the ocular surfaces of tens of thousands of patients in clinical practice, the authors can attest to the rarity of CL in the general population. These lesions usually occur due to lymphatic stasis from trauma, atopy or neoplastic disease.[15] We present the ocular findings and related symptoms for eight adult male and five adult female patients with classic FD, all of whom had received enzyme replacement therapy (ERT) for at least 4 years prior to evaluation.

## METHODS

### Examination and clinical findings

Slit lamp examinations were performed on the 13 adult patients, all of whom had received ERT (1 mg/kg every 2 weeks, except for patient 8, who received 0.5 mg/kg) for at least 4 years before the ocular examination. The average age was 48 years with a range of 35–55 years for men and 21–71 years for women. The mean duration of ERT was 8.4 years (men 8.9 years, women 7.6 years) with a range of 4–14 years. Classical Fabry mutations included Q283X, R227X, W236X and W277X.

A Haag-Streit BQ-900 Slit Lamp with EyeCap v7.x Imaging System (Haag-Streit International, Koeniz, Switzerland) including Release Module, Camera Module, and light-emitting diode (LED) light source was used to photograph the conjunctivae of all participants. Presence or absence of CL was determined according to the definition of Welch *et al*[15] by the primary evaluator (MDS) and was independently observed in each case from the images by a second observer (WJB). Clinical data for patients included age, duration of ERT, mutation status, ocular symptoms and presence of peripheral lymphoedema.

### Instrument settings and image capture

On the slit lamp, the 12.5× right eyepiece with reticle was focused, both eyepieces were adjusted for the examiner's refraction, and the manufacturer's white balance and filter checks were performed to maximise image quality. On the EyeCap computer, the camera exposure time was set to 33 ms. The slit illumination filter on the light tower was set to

**To cite:** Sivley MD, Wallace EL, Warnock DG, *et al*. *Br J Ophthalmol* 2018;**102**:54–58.

'clear' (brightest setting, no filter—pin set to far right or far left of examiner) for all images.

Diffuse and cross-sectional views of the bulbar conjunctivae were obtained. The manufacturer's recommended settings were altered in order to optimise these views. For diffuse views, the aperture stop was closed to optimise image quality. Magnification was set to 10× or 16×. On the instrument platform, background illumination was set to 15%–30% and slit beam illumination was turned off (set to zero). Beginning with the right eye, each patient was instructed to turn their eyes in the appropriate direction to image the temporal bulbar conjunctiva, followed by the inferior, superior and nasal bulbar conjunctivae. The same sequence was used to capture diffuse images on the left eye.

When CL was observed, a cross-sectional image of each lesion was attempted using the following settings: on the slit lamp tower, slit beam width was set to ≤0.2 mm, aperture stop to 4–6 mm, aperture to 1 and magnification to 16× or 25×. On the instrument platform, background illumination was set to 15%–30% and slit beam illumination to 50%–60%.

## RESULTS

CL was observed in 11 of the 13 subjects (85%) in this cohort. Clinical presentations of CL in this series included single and confluent fluid-filled cysts (figure 1), sausage-like beaded dilatations resembling a 'string of pearls' (figure 2) and areas of conjunctival oedema (figure 3). All lesions were located within 6 mm of the corneal limbus, within the pericorneal lymphatic ring.[15] The presence of bilateral corneal verticillata was confirmed in each patient (figure 4). CL prevalence and other patient characteristics of this cohort are summarised in table 1. The quantity, location and type of CL lesions are summarised in table 2.

Interestingly, six of the seven men with CL and one without CL had lymphoedema of the lower extremities. Five of the six men with peripheral lymphoedema also had eyelid oedema. Three of the women in this cohort had lower limb lymphoedema and one of these had eyelid oedema. Twelve of the patients, except the youngest woman, reported subjective complaints of dry eye and/or foreign body sensations similar to those associated with conjunctival cysts.[14] Other well-documented ocular manifestations of FD in this cohort included bilateral conjunctival vessel abnormalities (figure 3) and corneal verticillata (figure 4). Fabry-related cataracts were detected in 10 of 13 subjects (seven men, three women).

Additionally, 12 of the 13 patients in our cohort (92%) exhibited clinical signs associated with dry eye syndrome (DES). These included inflammatory eyelid disease (eg, blepharitis, meibomian gland dysfunction), superficial punctate keratitis, excessive watering of the eyes or a combination. Nine of the 12 with DES (75%) reported symptoms of foreign body sensation, chronic irritation and/or photophobia. Eight of the nine patients who were symptomatic for DES (89%) also had CL.

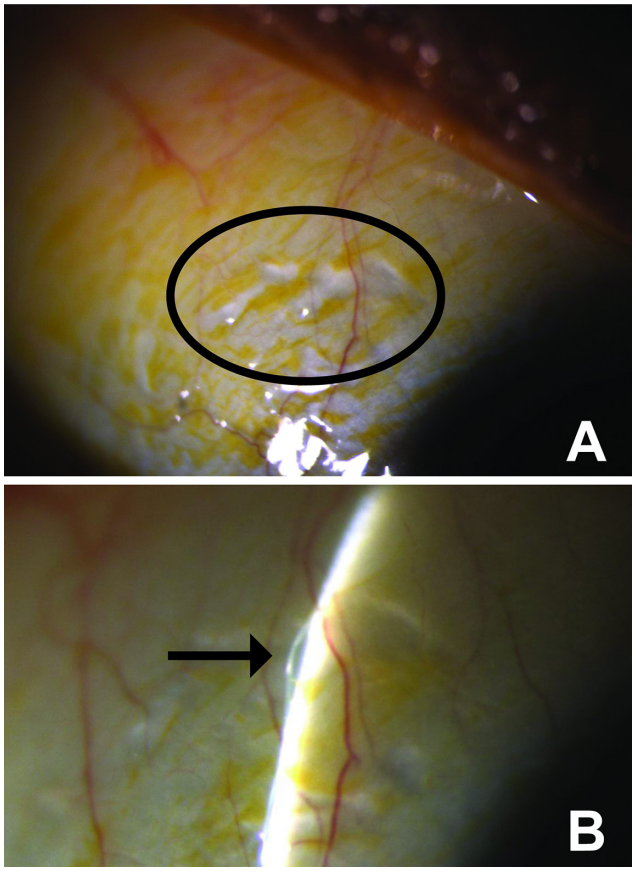


**Figure 1** Slit lamp views of conjunctival lymphangiectasia (CL) in Fabry disease. (A) Circled: Distended lymphatic channels on the bulbar conjunctival surface of patient 6. The surrounding yellow areas represent pooling of sodium fluorescein dye, which has been instilled topically to enhance the visibility of these elevated irregularities. (B) Arrow: Cross-sectional view of the same CL lesion shown in (A).

## DISCUSSION

Corneal lesions and conjunctival blood vessel abnormalities are common anterior segment findings in patients with classic FD,[6 16] but a literature search for CL associated with FD revealed only one report of chemosis.[17] Additionally, ocular symptoms associated with CL have not been emphasised and have not been addressed in overall assessments of Fabry symptomology or quality of life.[9 10] Dry eye symptoms were described in a survey examination of patients with FD.[8] Symptoms of DES may

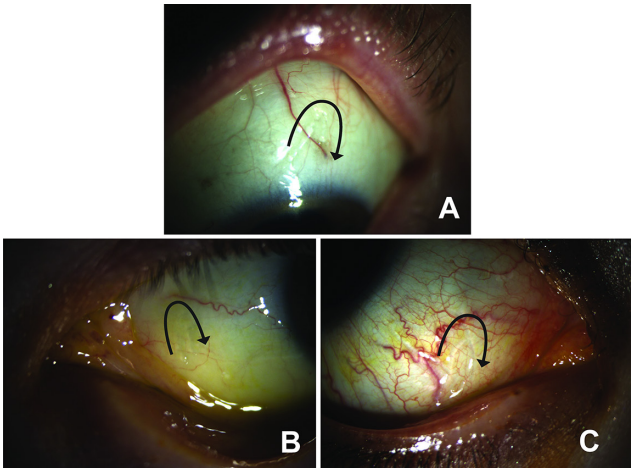


**Figure 2** Beaded dilatations resembling a 'string of pearls' on the bulbar conjunctival surfaces of patients 3, 5 and 11. The black arrows trace these linear elevations. (A): 'String of pearls' configuration within the superior conjunctiva of patient 11. (B): Conjunctival lymphangiectasia on the nasal bulbar conjunctiva of patient 3, enhanced with sodium fluorescein. (C): Intersecting lymphatic channels are visible on the inferior bulbar conjunctival surface of patient 5. A faint trace of sodium fluorescein remains.

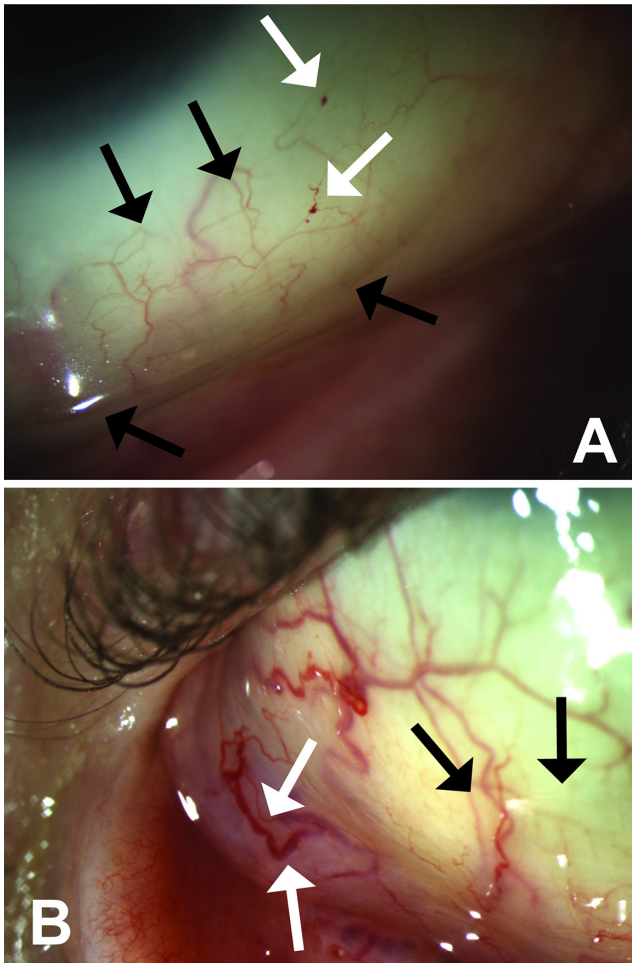


**Figure 3** Conjunctival lymphangiectasia shown as areas of oedema resembling focal chemosis within the lower conjunctivae of patients 1 and 4. (A): The black arrows surround an area of oedema in patient 1. White arrows indicate vascular anomalies known as telangiectasia, aneurysmal outpouchings of blood vessel walls within conjunctivae caused by reduced sympathetic tone of vascular smooth muscle in Fabry disease (FD). (B): Conjunctival oedema in patient 4 is indicated by the black arrows. White arrows here denote tortuosity and 'sausaging' of conjunctival blood vessels, a characteristic of FD.

be complicated by CL and corneal dysaesthesia resulting from small-fibre neuropathy in patients with FD.[18]

## Pathophysiology of CL

CL occurs when normal lymphatic vessels become distended and/or leak to create areas of lymphatic oedema within the bulbar conjunctivae. This uncommon condition typically occurs secondary to local lymphatic scarring or distal obstruction and can either be unilateral or bilateral.[15] CL accounts for 1% or less of conjunctival lesions in the general population and 5%–8% of all conjunctival cysts.[11–14] Lymphangiectasia of the conjunctiva occurs more commonly in middle-aged adults in response to IgE-mediated allergies, inflammatory or neoplastic diseases, organ transplant rejection or scarring from ocular trauma or surgery.[11 15 19] None of these conditions were identified in subjects with CL in this cohort, except patient 3, who underwent cataract extraction using sutureless corneal incisions (which eliminate trauma to conjunctivae, thus sparing conjunctival lymphatics).[20]

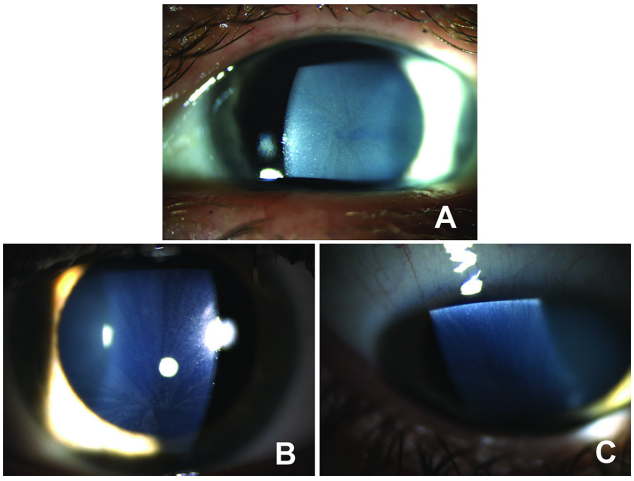


**Figure 4** Corneal verticillata (CV), the hallmark ocular sign of Fabry disease, was observed in all patients in this cohort. (A): CV with a central vortex, in patient 1. These lesions are commonly referred to as corneal 'whorls'. (B): CV with an inferior vortex, in patient 5. (C): Superior view of the cornea in (B), showing presumed migration of globotriaosylceramide from the limbal region.

The primary differential diagnosis for CL is epithelial inclusion cysts of the conjunctiva, which form when epithelial cells are displaced by trauma or inflammation and proliferate to form fluid-filled cavities. Unlike CL, inclusion cysts occur more commonly in the first 3 decades of life, tend to be larger and more bullous than lymphangiectasia and are prone to form near or within conjunctival fornices.[12]

Other potential diagnoses for CL include allergic conjunctivitis, cystic conjunctival nevi, conjunctivochalasis, hereditary lymphoedema syndromes, congenital lymphatic malformations, hypoproteinaemia, local venous hypertension, increased vascular permeability, inflammatory disorders, tumours, cancer metastasis, transplant rejection, conjunctival and eyelid surgeries and Loa loa infestations.[11 12 15 17 19 21 22] Based on case histories and clinical observations, these conditions were not thought to be present in the subjects with CL in this cohort.

## CL in FD

The pathophysiology of CL in FD is not known but may be related to lymphatic dysregulation considering lymphatic dysfunction in FD is well documented.[2] Amann-Vesti *et al*[23] demonstrated that lymphangiopathy of the skin in patients with FD is characterised by obliteration of lymphatic microvessels, microlymphatic hypertension and reduced lymph drainage capacity. Even when oedema is not clinically apparent, severe structural and functional changes are present in the initial lymphatics of the skin due to Gb-3 accumulation in FD.[23] Hence, possible mechanisms of CL are lymphatic vessel fragmentation and/or obstruction of lymphatic vasculature by Gb-3, resulting in leakage of lymph into conjunctival interstitium, or lymphatic stasis with visible vessel distention.

Interestingly, all lesions in the 11 patients with CL in this cohort were located within the lymphatic-rich perilimbal area of the bulbar conjunctivae, an observation which might further support the hypothesis that lymphatic vessel fragmentation or obstruction of lymphatic channels by Gb-3 lead to CL formation in FD.[15 23 24] Importantly, CL was detected in our patients despite long-term ERT, similar to the lack of response of peripheral lymphoedema to ERT.[2] A previous report[7] described two

**Table 1** Prevalence of conjunctival lymphangiectasia and other characteristics of adult patients with classic Fabry disease

| Subject | Gender (male/female) | GLA mutation | ERT (years) | Peripheral lymphoedema | Conjunctival lymphangiectasia | Dry eye |
|---|---|---|---|---|---|---|
| 1 | Male | R227X | 5 | Yes | Yes | Yes |
| 2 | Male | R227X | 14 | Yes | No | Yes |
| 3 | Male | R227X | 10 | Yes | Yes | Yes* |
| 4 | Male | R227X | 14 | Yes | Yes | Yes* |
| 5 | Female | R227X | 4 | No | Yes | No |
| 6 | Male | W277X | 5 | Yes | Yes | Yes* |
| 7 | Female | W277X | 7 | Yes | Yes | Yes* |
| 8 | Male | W277X | 4 | Yes | Yes | Yes* |
| 9 | Female | W277X | 8 | No | Yes | Yes* |
| 10 | Male | W236X | 10 | Yes | Yes | Yes* |
| 11 | Female | W236X | 9 | Yes | Yes | Yes* |
| 12 | Male | W236X | 9 | No | Yes | Yes |
| 13 | Female | Q283X | 10 | Yes | No | Yes* |

*Indicates additional presence of dry eye symptoms, such as chronic irritation and foreign body sensation.
GLA, alpha-galactosidase A locus; ERT, enzyme replacement therapy with agalsidase beta, peripheral lymphoedema in any extremity; dry eye findings included evaporative dry eye caused by inflammatory lid disease or reduced tear production.[26]

classic male patients who did not have corneal verticillata following 9 years of ERT but without baseline assessment and follow-up examinations. Therefore, the effects of ERT on the ocular findings in FD remain unclear.

Recent reports have re-emphasised the importance of corneal verticillata as an important disease-defining manifestation of FD.[7] The phenotypic variation of FD, especially in classic female patients and in patients with late-onset variants, is well appreciated. Currently, available biomarkers like lyso-Gb-3 may assist in the stratification of patients with FD.[25] Similarly, more extensive description and characterisation of the ocular findings in FD may improve the diagnostic criteria beyond the current binary assessment of the presence or absence of corneal verticillata.

**Table 2** Type and location of conjunctival lymphangiectasia lesions in this cohort

| Subject no | Eye (R/L) | Location | Type of lesion | Lesions (n) |
|---|---|---|---|---|
| 1 | R | Inferonasal | Diffuse | 1 |
| 2 | – | – | – | – |
| 3 | L | Nasal | SoP* | 1 |
| | | Inferonasal | Single cyst | 1 |
| 4 | R | Inferonasal | Diffuse | 1 |
| | L | Inferonasal | Single cyst | 1 |
| | | Superosemporal | Single cyst | 3 |
| 5 | R | Inferonasal | SoP* | 3 |
| 6 | R | Superotemporal | SoP* | 3 |
| 7 | R | Nasal | Single cyst | 1 |
| | | Inferonasal | Single cyst | 1 |
| 8 | R | Superonasal | Single cyst | 1 |
| 9 | R | Inferotemporal | Single cyst | 1 |
| | L | Temporal | Single cyst | 1 |
| 10 | R | Superior | SoP* | 1 |
| 11 | L | Superotemporal | SoP* | 1 |
| 12 | R | Temporal | Single cyst | 1 |
| | | Superotemporal | Single cyst | 1 |
| | | Inferotemporal | Diffuse | 1 |
| | L | Inferotemporal | Single cyst | 1 |
| 13 | – | – | – | – |

*SoP, String of Pearls (multiple connected cysts).
Note that subjects 5 and 6 had multiple Strings of Pearls (SoP).

In conclusion, conjunctival lymphangiectasia accounts for about 1% of all conjunctival lesions in the general population, making the finding of CL in 85% of this cohort much higher than expected. The concordance between peripheral lymphoedema and CL, and the poor response to long-term ERT, suggest a pathophysiological link between these two manifestations of FD. An association may also exist between CL and DES, the symptoms of which may be impacted by Fabry-related corneal dysaesthesia. Thus, it is important to take a thorough history of ocular symptoms and assess for DES in patients with FD.

The members of this cohort are patients with classic FD with varying degrees of renal, cardiac and central nervous system involvement, all treated with long-term ERT. Their clinical status is, therefore, fairly homogenous, making correlations between ocular and systemic conditions difficult to interpret. Identification of CL as an additional ocular manifestation of FD is important for all eye care providers, especially those who treat dry eye symptoms and anterior segment specialists who routinely scan the cornea and conjunctiva for blemishes due to contact lens wear or refractive surgery. Considering the persistence of CL and DES with long-term ERT, further studies are needed to evaluate the severity of all ocular complaints in FD, especially those associated with CL and the response to local therapy for DES in patients with FD.

**Acknowledgements** We thank Leslie Jackson and Christina Singleton for collection of patient information, and a very special thanks to our patients with FD and the following clinic coordinators who made their visits possible: Holly Barrow, Terin Dupre, Clara Edwards and Maria Voce.

**Contributors** MDS, ELW and DGW participated in data analysis, interpretation and writing of the manuscript. WJB participated in writing the manuscript.

**Competing interests** MDS is an employee of the University of Alabama at Birmingham and Cleveland Eye Care and has undertaken contracted research for Genzyme. ELW is an employee of the University of Alabama at Birmingham, received consulting fees from Genzyme and received fees directly for non-CME/CE services from Genzyme. DGW is an employee of the University of Alabama at Birmingham, received consulting fees from Genzyme, Actelion, Amicus and Protalix, received fees directly for non-CME/CE services from Genzyme and also has undertaken contracted research for Genzyme. WJB is an employee of the University of Alabama at Birmingham and Alabama Eye & Cataract Center, received consulting fees from Material Performance Assessments and has undertaken contracted research for Genzyme.

**Patient consent** Patient consent was not obtained since this article contains no identifiable images or personal medical information about any identifiable living or

deceased individual, and patient consent forms are not required according to patient consent and confidentiality policies of the BJO.

**Provenance and peer review** Not commissioned; externally peer reviewed.



## REFERENCES


1 Desnick RJ, Ioannou YA, Eng CM. Alpha-galactosidase A deficiency: Fabry disease. In: Scriver CBA, Sly W, Valle D, eds. *The metabolic bases of inherited disease*. 8th ed. New York: McGraw-Hill, 2001:3733–74.
2 Orteu CH, Jansen T, Lidove O, *et al*; FOS Investigators. Fabry disease and the skin: data from FOS, the Fabry outcome survey. *Br J Dermatol* 2007;157:331–7.
3 Ries M, Ramaswami U, Parini R, *et al*. The early clinical phenotype of Fabry disease: a study on 35 european children and adolescents. *Eur J Pediatr* 2003;162:767–72.
4 Eng CM, Fletcher J, Wilcox WR, *et al*. Fabry disease: baseline medical characteristics of a cohort of 1765 males and females in the Fabry registry. *J Inherit Metab Dis* 2007;30:184–92.
5 Samiy N. Ocular features of Fabry disease: diagnosis of a treatable life-threatening disorder. *Surv Ophthalmol* 2008;53:416–23.
6 Sivley MD. Fabry disease: a review of ophthalmic and systemic manifestations. *Optom Vis Sci* 2013;90:e63–78.
7 van der Tol L, Sminia ML, Hollak CE, *et al*. Cornea verticillata supports a diagnosis of Fabry disease in non-classical phenotypes: results from the dutch cohort and a systematic review. *Br J Ophthalmol* 2016;100:3–8.
8 Davey PG. Fabry disease: a survey of visual and ocular symptoms. *Clin Ophthalmol* 2014;8:1555–60.
9 Morier AM, Minteer J, Tyszko R, *et al*. Ocular manifestations of Fabry disease within in a single kindred. *Optometry* 2010;81:437–49.
10 Arends M, Hollak CE, Biegstraaten M. Quality of life in patients with Fabry disease: a systematic review of the literature. *Orphanet J Rare Dis* 2015;10:77.
11 Grossniklaus HE, Green WR, Luckenbach M, *et al*. Conjunctival lesions in adults. A clinical and histopathologic review. *Cornea* 1987;6:78–116.
12 Nath K, Gogi R, Zaidi N, *et al*. Cystic lesions of conjunctiva (a clinicopathogical study). *Indian J Ophthalmol* 1983;31:1–4.
13 Shields JA, Shields CL. Orbital cysts of childhood--classification, clinical features, and management. *Surv Ophthalmol* 2004;49:281–99.
14 Thatte S, Jain J, Kinger M, *et al*. Clinical study of histologically proven conjunctival cysts. *Saudi J Ophthalmol* 2015;29:109–15.
15 Welch J, Srinivasan S, Lyall D, *et al*. Conjunctival lymphangiectasia: a report of 11 cases and review of literature. *Surv Ophthalmol* 2012;57:136–48.
16 Pitz S, Kalkum G, Arash L, *et al*. Ocular signs correlate well with disease severity and genotype in Fabry disease. *PLoS One* 2015;10:e0120814.
17 Edwards JD, Bower KS, Brooks DB, *et al*. Fabry disease and chemosis. *Cornea* 2009;28:224–7.
18 Tavakoli M, Marshall A, Thompson L, *et al*. Corneal confocal microscopy: a novel noninvasive means to diagnose neuropathy in patients with Fabry disease. *Muscle Nerve* 2009;40:976–84.
19 Kerjaschki D. The lymphatic vasculature revisited. *J Clin Invest* 2014;124:874–7.
20 Al Mahmood AM, Al-Swailem SA, Behrens A. Clear corneal incision in cataract surgery. *Middle East Afr J Ophthalmol* 2014;21:25–31.
21 Awdry P. Lymphangiectasia haemorrhagica conjunctivae. *Br J Ophthalmol* 1969;53:274–8.
22 Shields JA, Eagle RC, Gausas RE, *et al*. Retrograde metastasis of cutaneous melanoma to conjunctival lymphatics. *Arch Ophthalmol* 2009;127:1222–4.
23 Amann-Vesti BR, Gitzelmann G, Widmer U, *et al*. Severe lymphatic microangiopathy in Fabry disease. *Lymphat Res Biol* 2003;1:185–9.
24 Kizhatil K, Ryan M, Marchant JK, *et al*. Schlemm's canal is a unique vessel with a combination of blood vascular and lymphatic phenotypes that forms by a novel developmental process. *PLoS Biol* 2014;12:e1001912.
25 Niemann M, Rolfs A, Störk S, *et al*. Gene mutations versus clinically relevant phenotypes: lyso-Gb3 defines Fabry disease. *Circ Cardiovasc Genet* 2014;7:8–16.
26 Tavares FP, Fernandes RS, Bernardes TF, *et al*. Dry eye disease. *Semin Ophthalmol* 2010;25:84–93.