Original Article

Ocular Manifestations of Fabry Disease: Report from a Tertiary Eye Care Center in Türkiye

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Abstract

Objectives: To report ocular manifestations in patients with Fabry disease (FD) from a tertiary eye care center in Türkiye.

Materials and Methods: This prospective, cross-sectional study included 30 eyes of 15 patients with FD. The diagnosis of FD was made based on a combination of clinical findings, genetic analysis, and biochemical evaluation. All participants underwent a detailed ophthalmic examination with special focus on the typical ocular features of FD (cornea verticillata, conjunctival aneurysms, cataract, retinal vessel tortuosity).

Results: The mean age was 45±17 years (range: 22-75 years), with a female/male ratio of 2:3. All patients had tortuous conjunctival vessels and 12 patients (80%) had conjunctival aneurysms. Cornea verticillata was present in 10 patients (66.6%), lens opacification in 4 patients (26.6%), and retinal vascular tortuosity in 8 patients (53.3%). All patients had at least two different ocular findings; most (3 heterozygotes/7 hemizygotes) had a combination of corneal verticillata and conjunctival vessel abnormality. The conjunctiva, cornea, and retina were affected together in 5 hemizygous patients (33.3%). One hemizygous patient had all FD-related ocular manifestations in both eyes.

Conclusion: To our knowledge, this study is the first to describe the ocular manifestations of FD in the Turkish population. Although cornea verticillata is considered a hallmark of FD, it was absent in approximately one-third of patients. Moreover, cataract, another well-known feature of FD, was present in only 26.6% of the patients. Conjunctival vascular abnormality alone seems to be quite rare in FD, although it often accompanies other ocular manifestations. Therefore, recognition of other mild findings and special consideration of their associations may increase the diagnostic value of ocular findings in FD.

Keywords: Cornea verticillata, conjunctival aneurysm, Fabry cataract, Fabry disease, metabolic diseases

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Introduction

Fabry disease (FD) is a rare X-linked lysosomal storage disorder with an estimated prevalence of 1/40,000-1/60,000 in males and 1/339,000 in females.[1] It is characterized by abnormal glycosphingolipid metabolism due to the absence or deficiency of the alpha-galactosidase A enzyme (α-Gal). Several mutations in the *α-Gal* gene (*GLA*) have been described in FD.[2,3] Affected males are defined as hemizygotes since they only have one disease-specific allele. As they usually have no detectable α-Gal enzyme activity, they exhibit the typical clinical picture of the disease more prominently. However, affected women are defined as heterozygotes. Unlike men, they show a wide spectrum of clinical manifestations, ranging from asymptomatic to advanced disease due to skewed X inactivation.[4,5]

Cardiopathy, neuropathy, and cerebrovascular diseases are the most serious clinical findings that increase morbidity and mortality in FD.[4,5] Although ophthalmologic involvement is also quite common in FD and is among the early manifestations of the disease, it is often overlooked. However, knowing the nature and frequency of ophthalmologic findings can be beneficial in the early and accurate diagnosis of FD.[6] Data on FD-associated ocular manifestations are limited in the literature, and available studies mostly involved patients from the USA, Canada, and European

countries.[7,8,9,10] Although there are some articles on FD in the Turkish population, to the best of our knowledge, there is no study specific to ophthalmologic involvement of the disease.[11,12] The aim of this study was to report the ophthalmological manifestations of patients with FD in a tertiary eye care center from Türkiye.

Materials and Methods

This prospective, cross-sectional study was carried out in accordance with the Declaration of Helsinki after approval by the Local Ethics Committee of Ege University (decision number: 24-1.1T/33, date: 25.01.2024). Informed consent was obtained from all participants.

Participants were recruited after referral from the Pediatric Metabolism and Nutrition Department and Medical Genetics Department of Ege University. All patients were diagnosed with FD and were referred to the Ege University Ophthalmology Department as a part of a comprehensive systemic examination. The diagnosis was made based on a combination of clinical findings, molecular genetic analysis, and biochemical evaluation.

A comprehensive case history of systemic findings and demographic data such as age and sex were recorded. All patients underwent a detailed ophthalmological evaluation, including anterior segment examination under slit lamp biomicroscopy, intraocular pressure measurement with Goldmann applanation tonometry, and fundus examination under pupil dilatation (after instillation of one drop of tropicamide 1% [Tropamid 1%, Bilim Pharmaceuticals, Türkiye]). Typical clinical features of FD such as cornea verticillata, conjunctival aneurysms, conjunctival vessel tortuosity, presence and type of lens opacification, and retinal vessel tortuosity were specifically analyzed. Best corrected visual acuities (BCVAs) were recorded as logarithm of the minimum angle of resolution (LogMAR). Tear film break-up time (TBUT) and Schirmer 1 tests were performed for the diagnosis of dry eye.

Patients with chronic systemic disease unrelated to FD (including connective tissue disorders, diabetes, etc.), who were receiving any topical or systemic treatments related to other diseases, and had a history of ocular trauma or concomitant ocular diseases were not included.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were given as mean, standard deviation, median, minimum, maximum, number, and percentage.

Results

Thirty eyes of 15 patients with ocular manifestations associated with FD were included. The mean age was 45±17 years (range, 22-75 years), with a female to male ratio of 2:3 (Table 1).

Case histories revealed that 4 patients (26.6%) had a family history of FD. Four out of 6 heterozygote women were asymptomatic. The number and severity of systemic involvements of FD (cardiac, renal and neurological) were higher in the hemizygote men than in the women. In 9 patients (60%), α-Gal activity was found to be low in biochemical analysis, and genetic analysis strengthened the diagnosis. In the remaining 6 patients (40%), α-Gal activity was within normal limits and the diagnosis of FD was confirmed by the presence of *GLA* mutation in genetic analysis. One patient was already under enzyme replacement therapy (ERT) when he was examined for ophthalmological manifestations.

The mean BCVA was 0.03±0.06 LogMAR (range, 0-0.2 LogMAR).

Conjunctival vessel changes constituted the most frequent ophthalmological findings of FD. Increased tortuosity of the bulbar conjunctival vessels was bilaterally present in all patients. In addition, conjunctival saccular aneurysms were also evident in 24 eyes of 12 patients (80%) (Figure 1A).

Cornea verticillata was present in 20 eyes of 10 patients (66.6%) (Figure 2).

Lens opacification was observed in 4 (26.6%) of the 15 patients. The median age of patients with lens opacification was 38.5 years (mean, 40.2; standard deviation, 16.4; range, 22-62 years). One of them had bilateral "spoke-like" cataract located at the level of the posterior lens capsule, consistent with the typical "Fabry cataract" (Figure 1B). The patient's visual acuity was affected bilaterally (right: 0.20; left: 0.10 LogMAR). One patient had bilateral sectoral, wedge-shaped, white cataract at the level of the anterior subcapsular area, with non-affected visual acuity (0.00 LogMAR in both eyes). Two patients had blue-dot (cerulean) cataract. One had bilateral symmetrical opacifications at the lens periphery, and visual acuities were not affected (0.00 LogMAR in both eyes). The other patient had a BCVA of 0.20 LogMAR in the eye with cataract, and the fellow eye was pseudophakic (operated elsewhere) at 39 years of age. There was no significant difference in terms of age between patients with and without cataracts ($p>0.05$).

Vascular tortuosity was the most common retinal finding, present in 8 (53.3%) out of 15 patients. These changes were bilateral and symmetrical in all patients (Figure 3).

All patients had at least two different ocular findings of FD; 66.6% (3 heterozygous females and 7 hemizygous males) had a combination of corneal verticillata and conjunctival vessel abnormality. Conjunctiva, cornea and retina were affected together in 5 patients (33.3%), and all were hemizygous males. All Fabry-related ocular findings, including cornea verticillata, conjunctival vessel abnormalities, cataract, and retinal vascular tortuosity were bilaterally present in only 1 hemizygous male patient.

The mean TBUT was 8±3 s (range, 4-10 s). The mean Schirmer 1 result was 26.3±5.4 mm (range, 19-30 mm). Bilateral dry eye was present in one patient. Preservative-free artificial tear drops (Eyestil SD, Sifi, Italy) were initiated.

Discussion

FD is an extremely rare, inherited lysosomal storage disorder that affects numerous organs. The main life-threatening manifestations are cardiopathy, neuropathy, and cerebrovascular diseases.[13,14] Although ophthalmologic involvement in FD is not negligible, it is often underestimated because it is characterized by mild visual symptoms and signs. Therefore, data on FD-related ophthalmologic manifestations are quite limited,

Table 1. Characteristics of the patients

Patient number	Age at diagnosis (years)	Male (M)/ female (F)	Cornea verticillata	Conjunctival tortuosity	Saccular conjunctival dilatations	Cataract	Retinal tortuosity	Mutation	ACMG classification
P1	25	M	+	+	+	-	+	p.P112L (c.335G>T)	Likely pathogenic
P2	75	M	+	+	+	-	+	p.P112L (c.335G>T)	Likely pathogenic
P3	52	M	+	+	+	-	-	p.G328V (c.983 G>T)	Pathogenic
P4	28	M	+	+	+	-	+	p.R342X (c.1024C>T)	Pathogenic
P5	22	F	+	+	+	+	-	c.963_964delinsCA (p.Q321_D322_delins HN)	Variant of unknown significance
P6	38	M	+	+	+	+	+	c.719_720insA (p.S241EfsX9)	Likely pathogenic
P7	62	F	-	+	+	+	-	p.A143T (c.427G>A)*	Likely pathogenic
P8	44	M	-	+	+	-	-	p.A143T (c.427G>A)*	Likely pathogenic
P9	54	M	+	+	+	-	-	p.Y216C (c.647A>G)	Pathogenic
P10	34	M	+	+	+	-	+	p.R227X (c.679C>T)	Pathogenic
P11	39	F	-	+	+	+	+	p.R118C (c.352C>T)	Likely pathogenic
P12	74	F	+	+	-	-	-	p.Y216C (c.647A>G)	Pathogenic
P13	38	F	-	+	-	-	-	p.A143T (c.427G>A)*	Likely pathogenic
P14	62	F	+	+	+	-	+	p.R227X (c.679C>T)	Pathogenic
P15	31	M	-	+	-	-	+	p.A143T (c.427G>A)*	Likely pathogenic

*At the time of diagnosis of the patients this variant was accepted to be a disease causing variant but in the recent classifications this variant is accepted as a "benign" variant (PMID: 37937776).
ACMG: American College of Medical Genetics and Genomics

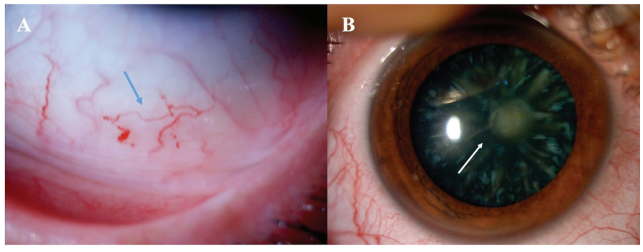

Figure 1. Representative photographs of ocular manifestations in Fabry patients. (A) Blue arrow indicates conjunctival vascular tortuosity and aneurysmal dilatations, (B) white arrow indicates Fabry cataract

and the available studies in the literature are mostly from the USA, Canada, and Europe.[7,8,9,10]

Ethnicity is a significant modifier in hereditary diseases and can strongly influence the characteristics of the disease. Therefore, studies with FD patients originating from different countries do not always reflect the entire population.[9,15] Comprehensive studies on FD from Türkiye are mostly in the fields of cardiology, nephrology, and neurology, and data on ophthalmologic involvement is very limited.[11,12,16,17] İnan et al.[17] evaluated peripheral nervous system involvement in 14 patients with FD and reported that half of the patients had additional ophthalmological findings, including cornea verticillata (2 patients) and retinal vascular tortuosity (2 patients). In a recent consensus statement, Ezgu et al.[18] conveyed Türkiye's multidisciplinary perspective on FD. Although they mentioned

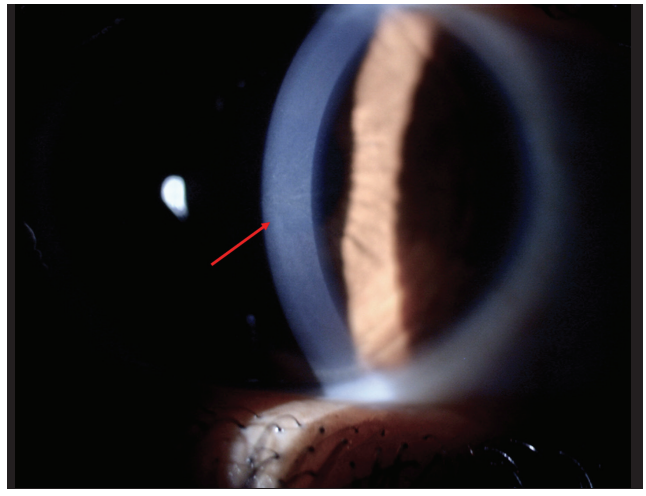

Figure 2. Cornea verticillata in a patient with Fabry disease. Red arrow indicates whorl-like gray opacities irradiating from the central cornea

the characteristic features of ophthalmologic involvement in their review, they did not make a population-based assessment of its prevalence.[18] Moreover, ophthalmological studies of FD in the Turkish population have mostly focused on microvascular signs of ocular involvement before visible symptoms appear.[19,20,21,22] In summary, although there are various studies on FD among the Turkish population, there is a lack of detailed and specific data on the nature and frequency of ophthalmologic findings of FD.

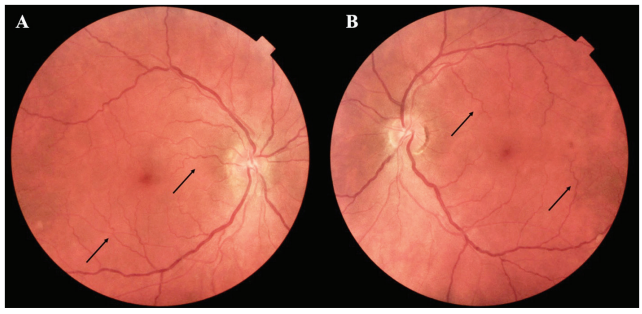

Figure 3. (A) Right and (B) left eye of a patient with Fabry disease. Black arrows show increased retinal vascular tortuosity, which is more evident at the posterior pole

To the best of our knowledge, this study is the first to specifically describe the nature and frequency of ocular manifestations of FD in the Turkish population.

The diagnosis of FD is challenging and often delayed, especially in cases without a clear family history. Fuller et al.[23] reported that the diagnosis of FD was made years after symptom onset (approximately 16 years in women and 14 years in men). In the natural course of FD, accumulation of undegraded glycosphingolipids causes progressive cell damage and eventual failure of organs such as the kidneys, heart, and the central and peripheral nervous systems. Therefore, delay in diagnosis is associated with further damage to the affected organs and causes an increased risk of morbidity and mortality.[24] Moreover, FD is one of the rare genetic lysosomal storage diseases with a medical treatment option. The widespread use of ERT, a major breakthrough in its treatment, has reinforced the importance of early detection of FD.[25,26,27] A high index of suspicion for FD is essential for timely recognition, but whole-population screening is not very cost-effective as it is an incredibly rare clinical condition.[28,29]

The presence of ophthalmological findings gains importance here by providing important clues to the clinician. Ocular manifestations are one of the first observable findings of FD, and slit-lamp examination alone is often sufficient to identify the findings. Therefore, it is critical for an ophthalmologist to know the nature, frequency, and possible consequences of ocular manifestations of FD.[6,30] Typical ophthalmologic features are conjunctival vascular abnormalities (vascular aneurysms and tortuosity), cornea verticillata, cataract, retinal vessel tortuosity, and rarely retinal vascular occlusion.[31,32,33,34] The incidence of each is reported at varying rates in studies conducted in different regions.[8,9,10,35] Nguyen et al.[7] reported from Australia that bulbar conjunctival vascular abnormality (97.1% in hemizygotes and 78.1% in heterozygotes) is the most common ophthalmologic manifestation in patients with FD, followed by cornea verticillata (94.1% in hemizygotes, 71.9% in heterozygotes) and retinal vascular tortuosity (76.5% in hemizygotes, 18.8% in heterozygotes).[7] Similarly, in a longitudinal study conducted in Canada, the most common ocular findings were reported as conjunctival vascular tortuosity (85.7%) and cornea verticillata (89.2%).[8] Consistent with the literature, in the present study, conjunctival vascular tortuosity (100%) and aneurysmal dilatations (80%) were the most frequent ocular signs of FD, followed by cornea verticillata (66.6%).

Cornea verticillata is considered to be the hallmark of FD and is a well-known manifestation of the disease. It is characterized by whorl-like opacities concentrated in the epithelial and subepithelial layers of the cornea and is typically bilateral.[32,36] Although cornea verticillata is highly suggestive of FD, it may also occur secondary to pharmacological (e.g., amiodarone, chloroquine, hydroxychloroquine) and non-pharmacological (e.g., multiple myeloma) etiologies.[37] In the literature, cornea verticillata has been reported at a frequency ranging from 43.7% to 94.5% in patients with FD.[8,9] This diversity may be related to the age, genotypes, and ethnicities of the patients, as well as to the subjectivity of the clinician's assessment. In the present study, approximately one-third of the patients did not have cornea verticillata. However, conjunctival vascular abnormalities were detected in a significant proportion of the patients. Although cornea verticillata is considered to be the most distinctive ophthalmologic finding of FD, it may not be present in every patient. Therefore, it is important to recognize other mild and easily overlooked findings of FD in addition to already well-known classical findings.

Cataract is another classical manifestation of FD which, unlike other findings, causes symptoms such as decreased vision and dysphotopsia. Theoretically, subcapsular lens opacification with a spoke-like appearance at the posterior capsule is defined as typical "Fabry cataract". In addition, cataract may present as a wedge-shaped white deposit at the anterior subcapsular level in FD.[7,8] However, the incidence of cataract is lower compared to other ophthalmological features.[9] In a multicenter study conducted across Europe, Fabry cataracts were reported in 9.8% of heterozygotes and 23.1% of hemizygotes.[9] Higher rates of cataract were reported from Canada (67.7%) and Australia (62.4%), although still relatively low compared to other ophthalmologic manifestations.[7,8] In the current study, the least common ophthalmologic manifestation was cataract, with a rate of 26.6%. The lower rate of cataract in this study can be explained by the sex distribution, as 40% of patients were female heterozygotes. Because FD is an X-linked inherited disease, sex disparity strongly affects the disease characteristics. As a general rule, FD symptoms are more pronounced in men due to the greater disease severity.[14,31] This sex difference may be more decisive and striking in cataract, which has a lower incidence compared to other ocular findings of FD.

Different ocular structures can be affected in FD. Therefore, the coexistence of multiple ophthalmologic findings is not uncommon. In fact, conjunctival vascular tortuosity rarely occurs in isolation in FD and is usually associated with other ocular findings.[9] Sodi et al.[9] reported local associations of tortuous vessels with cornea verticillata or cataract in FD. This coexistence seems to be more prominent in males. Consistent with this, all participants in the current study had at least two detectable ocular findings, most of which were a combination of corneal verticillata and conjunctival vessel abnormalities. In addition,

the coexistence of three or more clinical features was observed in 33.3% of the patients and all of them were male. This supports that sex differences also affect the number of ophthalmological areas affected. In parallel with other systemic involvements, typical ophthalmological manifestations of FD can be seen more frequently and more prominently in men.

Dry eye syndrome (DES) is a multifactorial disease that accompanies a significant proportion of systemic diseases. It has been suggested that the accumulation of abnormal deposits in the autonomic ganglia and lacrimal glands may lead to diminished lacrimal gland function.[31,38] Consequently, it has been hypothesized that the frequency of DES increases in FD due to decreased tear secretion.[30,31] Davey[30] reported in a visual symptom survey analysis that FD patients had significantly more "dryness" symptoms compared to healthy individuals. Moreover, Bitirgen et al.[20] showed corneal nerve fiber damage, reduced corneal sensitivity, and increased dendritic cells in patients with FD using in vivo confocal microscopy. Although all these data support an association between dry eye and FD, the nature of their relationship remains controversial. In the present study, DES was present in only one patient, who was misdiagnosed as having a rheumatologic disease. Further studies are still needed to reach a clear conclusion about DES in FD.

Study Limitations

The main limitations of this study are the small number of subjects included and the subjective evaluation of the findings. Measurable, precise parameters are not available yet, so potential interobserver differences in the evaluation of FD-related ocular findings are inevitable. Further studies with a population-based, multicenter design and more participants are still needed to clearly define the ophthalmological features of FD. In addition, this study presents the ophthalmological clinical picture in a single time frame, immediately after the diagnosis of FD. However, a longitudinal study to see whether the ocular findings change over time will be more valuable.

Conclusion

In conclusion, slit-lamp examination alone is usually sufficient to identify the ocular findings and guide the diagnosis of FD, especially when there is clinical suspicion. Awareness among ophthalmologists about the nature and frequency of FD-related findings may be helpful in early and accurate diagnosis. Ethnicity is the major modifier in hereditary diseases, and FD-related ophthalmologic manifestations may vary in populations originating from different regions. To the best of our knowledge, there is no previous report of ophthalmologic involvement of FD in the Turkish population. Although cornea verticillata is considered to be the most distinctive and prevalent ophthalmologic manifestation of FD, approximately one-third of the patients did not have corneal verticillata in the present study. Furthermore, cataract, another well-known feature of FD, was present in only 26.6% of the patients. Therefore, in addition to well-known specific findings, recognition of other mild findings and special consideration of their local associations may increase the diagnostic value of ocular manifestations in FD.

Ethics

Ethics Committee Approval: Approval by the Local Ethics Committee of Ege University (decision number: 24-1.1T/33, date: 25.01.2024).

Informed Consent: Obtained.

Authorship Contributions

Surgical and Medical Practices: S.K.U., H.O., E.Y.S., M.Ç., M.P., Concept: M.P., H.O., Design: İ.K., M.P., H.O., Data Collection or Processing: İ.K., S.K.U., E.Y.S., Analysis or Interpretation: H.O., M.Ç., M.P., Literature Search: İ.K., M.P., Writing: İ.K., M.P., H.O.

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References

1. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. J Med Genet. 2001;38:769-775.
2. Germain DP. Fabry disease: recent advances in enzyme replacement therapy. Expert Opin Investig Drugs. 2002;11:1467-1476.
3. Zarate YA, Hopkin RJ. Fabry's disease. Lancet. 2008;372:1427-1435.
4. Bernardes TP, Foresto RD, Kirsztajn GM. Fabry disease: genetics, pathology, and treatment. Rev Assoc Med Bras (1992). 2020;66 (Suppl 1):s10-s16.
5. Schiffmann R, Fuller M, Clarke LA, Aerts JM. Is it Fabry disease? Genet Med. 2016;18:1181-1185.
6. Samiy N. Ocular features of Fabry disease: diagnosis of a treatable life-threatening disorder. Surv Ophthalmol. 2008;53:416-423.
7. 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 Exp Ophthalmol. 2005;33:164-168.
8. Michaud L. Longitudinal study on ocular manifestations in a cohort of patients with Fabry disease. PLoS One. 2019;14:e0213329.
9. Sodi A, Ioannidis AS, Mehta A, Davey C, Beck M, Pitz S. Ocular manifestations of Fabry's disease: data from the Fabry Outcome Survey. Br J Ophthalmol. 2007;91:210-214.
10. Orssaud C, Dufier J, Germain D. Ocular manifestations in Fabry disease: a survey of 32 hemizygous male patients. Ophthalmic Genet. 2003;24:129-139.
11. Barman HA, İkitimur B, Kılıçkıran Avcı B, Durmaz E, Atıcı A, Aslan S, Ceylaner S, Karpuz H. The Prevalence of Fabry Disease Among Turkish Patients with Non-Obstructive Hypertrophic Cardiomyopathy: Insights from a Screening Study. Balkan Med J. 2019;36:354-358.
12. Tomar ÖK, Bal AZ, Şirali SK, Duranay M, Korucu B, Güz G, Akdağ Sİ. The prevalence of Fabry disease in a Turkish population with chronic kidney patients. Int Urol Nephrol. 2023;55:1629-1634.
13. Gibas AL, Klatt R, Johnson J, Clarke JT, Katz J. Disease rarity, carrier status, and gender: a triple disadvantage for women with Fabry disease. J Genet Couns. 2008;17:528-537.
14. Mehta A, Ricci R, Widmer U, Dehout F, Garcia de Lorenzo A, Kampmann C, Linhart A, Sunder-Plassmann G, Ries M, Beck M. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. Eur J Clin Invest. 2004;34:236-242.
15. Pitz S, Kalkum G, Arash L, Karabul N, Sodi A, Larroque S, Beck M, Gal A. Ocular signs correlate well with disease severity and genotype in Fabry disease. PLoS One. 2015;10:e0120814.
16. Erol Ç. Artificial Intelligence, Fabry Disease…. Anatol J Cardiol. 2023;27:178.
17. İnan R, Meşe M, Bicik Z. Multidisciplinary approach to Fabry disease: from the eye of a neurologist. Acta Neurol Belg. 2020;120:1333-1339.

18. Ezgu F, Alpsoy E, Bicik Bahcebasi Z, Kasapcopur O, Palamar M, Onay H, Ozdemir BH, Topcuoglu MA, Tufekcioglu O. Expert opinion on the recognition, diagnosis and management of children and adults with Fabry disease: a multidisciplinary Turkey perspective. Orphanet J Rare Dis. 2022;17:90.
19. Cakmak AI, Atalay E, Cankurtaran V, Yaşar E, Turgut FH. Optical coherence tomography angiography analysis of fabry disease. Int Ophthalmol. 2020;40:3023-3032.
20. Bitirgen G, Turkmen K, Malik RA, Ozkagnici A, Zengin N. Corneal confocal microscopy detects corneal nerve damage and increased dendritic cells in Fabry disease. Sci Rep. 2018;8:12244.
21. Yanık Ö, Çıkı K, Özmert E, Sivri S. Vascular and structural analyses of retinal and choroidal alterations in Fabry disease: the effect of hyperreflective foci and retinal vascular tortuosity. Ophthalmic Genet. 2022;43:344-353.
22. Cankurtaran V, Tekin K, Cakmak AI, Inanc M, Turgut FH. Assessment of corneal topographic, tomographic, densitometric, and biomechanical properties of Fabry patients with ocular manifestations. Graefes Arch Clin Exp Ophthalmol. 2020;258:1057-1064.
23. Fuller M, Meikle PJ, Hopwood JJ. Epidemiology of lysosomal storage diseases: an overview. In: Mehta A, Beck M, Sunder-Plassmann G, editors. Fabry Disease: Perspectives from 5 Years of FOS. Oxford: Oxford PharmaGenesis; 2006.
24. Aerts JM, Groener JE, Kuiper S, Donker-Koopman WE, Strijland A, Ottenhoff R, van Roomen C, Mirzaian M, Wijburg FA, Linthorst GE, Vedder AC, Rombach SM, Cox-Brinkman J, Somerharju P, Boot RG, Hollak CE, Brady RO, Poorthuis BJ. Elevated globotriaosylsphingosine is a hallmark of Fabry disease. Proc Natl Acad Sci U S A. 2008;105:2812-2817.
25. El Dib R, Gomaa H, Carvalho RP, Camargo SE, Bazan R, Barretti P, Barreto FC. Enzyme replacement therapy for Anderson-Fabry disease. Cochrane Database Syst Rev. 2016;7:CD006663.
26. Schiffmann R, Kopp JB, Austin HA 3rd, Sabnis S, Moore DF, Weibel T, Balow JE, Brady RO. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. JAMA. 2001;285:2743-2749.
27. Turkmen K, Baloglu I. Fabry disease: where are we now? Int Urol Nephrol. 2020;52:2113-2122.
28. Linthorst GE, Bouwman MG, Wijburg FA, Aerts JM, Poorthuis BJ, Hollak CE. Screening for Fabry disease in high-risk populations: a systematic review. J Med Genet. 2010;47:217-222.
29. van der Tol L, Smid BE, Poorthuis BJ, Biegstraaten M, Deprez RH, Linthorst GE, Hollak CE. A systematic review on screening for Fabry disease: prevalence of individuals with genetic variants of unknown significance. J Med Genet. 2014;51:1-9.
30. Davey PG. Fabry disease: a survey of visual and ocular symptoms. Clin Ophthalmol. 2014;8:1555-1560.
31. Sivley MD. Fabry disease: a review of ophthalmic and systemic manifestations. Optom Vis Sci. 2013;90:e63-78.
32. Degirmenci C, Yilmaz SG, Onay H, Palamar M, Ucar SK, Kayikcioglu M, Coker M. A novel mutation and in vivo confocal microscopic findings in Fabry disease. Saudi J Ophthalmol. 2017;31:45-47.
33. Oto S, Kart H, Kadayifçilar S, Ozdemir N, Aydin P. Retinal vein occlusion in a woman with heterozygous Fabry's disease. Eur J Ophthalmol. 1998;8:265-267.
34. Ersoz MG, Ture G. Cilioretinal artery occlusion and anterior ischemic optic neuropathy as the initial presentation in a child female carrier of Fabry disease. Int Ophthalmol. 2018;38:771-773.
35. Nguyen ATM, Chamberlain K, Holland AJA. Paediatric chemical burns: a clinical review. Eur J Pediatr. 2021;180:1359-1369.
36. van der Tol L, Sminia ML, Hollak CE, Biegstraaten M. 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.
37. Sahyoun JY, Sabeti S, Robert MC. Drug-induced corneal deposits: an up-to-date review. BMJ Open Ophthalmol. 2022;7:e000943.
38. Cable WJ, Kolodny EH, Adams RD. Fabry disease: impaired autonomic function. Neurology. 1982;32:498-502.