TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Original Article

Evaluation of Hearing and Auditory Pathways in Fabry Disease Patients

Fethi YÖNET[1], İsmail BALOĞLU[2], Çiğdem KUCUR YÖNET[3], Mehmet Akif DÜNDAR[4], Hakan OZER[5], Yasin ÖZTÜRK[5], Kültigin TÜRKMEN[2]

[1]Division of Nephrology, Department of Internal Medicine, Necmettin Erbakan University, Konya Turkey
[2]Department of Nephrology, Necmettin Erbakan University Meram School of Medicine, Konya Turkey
[3]Department of Internal Medicine, Konya City Hospital, Konya Turkey
[4]Department of Otorhinolaryngology, Necmettin Erbakan University, Meram School of Medicine, Konya, Turkey
[5]Department of Nephrology, Meram School of Medicine, Necmettin Erbakan University, Konya, Turkey

ABSTRACT

Background Hearing and the auditory pathway are affected in Fabry diseases (FD). There is limited data on hearing and auditory pathways in this population. Therefore, we aimed to investigate auditory functions and auditory pathways using auditory brainstem responses (ABR), otoacoustic distortion emission (DPOAE), pure tone audiometry (PTA), and tympanometry in patients with FD and to compare these results with those of healthy individuals.

Material and Methods This study included 16 patients with FD (F/M: 8/8, age: 33.5 ± 15.4 years) and 16 healthy controls (F/M: 5/11, age: 33.6 ± 6.3 years). Hearing functions and auditory pathways were assessed with ABR, DPOAE, PTA, and tympanometry.

Results According to the results of PTA, conductive hearing loss was detected in 4 (25%) of the patients with FD. When the 500-4,000 Hz frequencies were assessed, the bone pathway hearing threshold in both ears was significantly higher in the patients with FD than in the control group ($p = 0.014$ and$p = 0.014$, respectively). When we compared the DPOAE measurements of the patients with FD and the control groups, the dB value measured at 2.8 kHz was significantly lower in the patient group than in the control group ($p = 0.018$). When we compared the ABR measurements, the right ear's 3-5 interpeak latency at 60 dB was significantly lower in the patient with FD than in the control group (1.8 ± 0.3 ms vs 2 ± 0.2 ms, $p = 0.033$).

Conclusions We found that the hearing loss rate and hearing threshold were statistically significantly higher in FD patients than in the control group. Hearing screening should be systematically performed in these patients.

Turk J Int Med 2023:5(2);84-91
DOI: 10.46310/tjim.1209122

Keywords: *Fabry disease, hearing, auditory pathways.*

Received: November 25, 2022; Accepted: January 29, 2023; Published Online: April 29, 2023

Address for Correspondence:
Fethi Yonet, M.D.
Division of Nephrology, Department of Internal Medicine, Necmettin Erbakan University, Konya, Turkey
E-mail: dr.fyonet@gmail.com

INTRODUCTION

The most common diseases among lysosomal storage diseases are Gaucher and Fabry diseases. The disease results from the deposition of globotriaosylceramide (Gb3) in various tissues due to insufficiency of the enzyme α-galactosidase A. Numerous signs of the disease may occur due to the deposition of Gb-3 in autonomic and spinal ganglia, renal tubulointerstitial cells and, renal glomerular, vascular smooth muscle cells, cardiac myocytes, vascular and lymphatic endothelial cells in the cornea.[1] Early clinical manifestations of the disease include hypohidrosis, gastrointestinal symptoms (GIS), angiokeratomas, distal joint pain, and tinnitus. The most important predictor of the likelihood of developing Fabry-related complications is enzyme activity.[2] However, even if distinctive signs and symptoms occur, there is a significant delay in diagnosis up to 20 years from the onset of symptoms. This is probably due to a lack of awareness and the wide range of clinical manifestations, especially in women.[3,4] Therefore, recognizing the signs and symptoms of Fabry disease (FD) is closely associated with disease awareness among paediatricians, pediatric metabolic specialists, pediatric geneticists, cardiologists, neurologists, dermatologists, nephrologists, trained pathologists, and ophthalmologists. In particular, after diagnosis, it is possible to change the disease's natural course and progression and improve patients' quality of life through treatment.[5,6] Nowadays, there is no curative treatment for FD. Recombinant α-Gal A and migalastat are treatment options for suitable patients.[7]

Patients with FD experience progressive hearing problems. These hearing problems, especially hearing loss, may develop gradually or occur suddenly. Symptomatic hearing loss happens in %18-55 of patients with FD, but sudden hearing loss occurs in %6-36 and tinnitus in %17-53 of patients. Typically, it is observed more frequently and to a greater extent in male FD patients. Recent studies have shown that the developing hearing loss in these patients is predominantly sensorineural.[8] However, this population has limited data on hearing and auditory pathways. Therefore, we aimed to investigate auditory functions and auditory pathways using auditory brainstem responses (ABR), pure tone audiometry (PTA), otoacoustic distortion emission (DPOAE), and tympanometry in patients with FD and to compare these results with those of healthy individuals.

MATERIAL AND METHODS

The protocol of the study was approved by the Medical Ethics Committee of Necmettin Erbakan University (NEU) (Faculty of Medicine, Konya, Turkey). The patients and healthy volunteers signed the written informed consent. This study included 16 patients with FD (F/M: 8/8, age: 33.5 ± 15.4 years) and 16 healthy controls (F/M: 5/11, age: 33.6 ± 6.3 years). In addition, we categorised patients according to whether they received treatment. Patient's medical records (information on patients' age, medications taken, duration and course of disease, and otologic history) were reviewed. Inclusion criteria were 1) 18-70 years of age, 2) decreased (< 2.5 nmol/mL/hour) α-gal-A activity in dried blood spots (DBS) in male patients, and 3) presence of GLA gene mutation associated with FD in female patients.

The screening of FD was performed by assessing α-gal-A activity < 2.5 nmol/mL/hour in DBS and was confirmed by GLA gene mutation analysis. The criteria for the diagnosis of FD were α-gal-A activity < 2.5 nmol/mL/hour in male patients and a genetic mutation associated with FD in female patients. The screening of FD was performed by assessing α-Gal A activity in dried blood spots (DBS) and was confirmed by GLA gene mutation analysis. GLA gene was sequenced using the MiSeq next-generation sequencing (NGS) platform, an FDA-approved diagnostic system (Illumina, San Diego, CA, USA). Plasma lyso-Gb3 levels were measured via tandem mass spectrometry method from DBS before ERT at the beginning and end of the study. Diagnostic procedures have been rearranged by adding them to the material method section.

A complete oto-rhino-larygologic examination was performed on all participants. Otologic history was obtained from all patients, including inherited deafness, otologic symptoms, otologic trauma or surgery, use of ototoxic agents, and noise exposure. All patients underwent otoscopy. None of the patients was found to have comorbidities related to otolaryngology in their history or on examination. Our patients had no middle ear problem, and no issues were found in the external auditory meatus and inner ears in the otolaryngologic test. In addition, otolaryngologic anamnesis and history showed no abnormality in their ears. Hearing functions and auditory pathways were assessed with ABR (Eclipse Interacoustics), DPOAE

(Otodynamics Echoport ILO 288 USB), PTA (Interacoustics AC33 Audiometer), and tympanometry (Interacoustics AT235). Tympanograms of all patients were also found to be Type A-Normal.

Air conduction and bone conduction hearing thresholds were calculated for each ear using a 5-dB stepwise method at 250, 500, 1000, 2000, 4000, and 8000 kHz. The severity of hearing loss was determined as PTA for 0.5, 1, 2, and 4 kHz. In addition, a high-frequency hearing loss (hFhl) was considered at 4 and 8 kHz to assess the inner ear's involvement better.

ABR measurements were performed on both ears separately with single-channel electrode placement. While subjects were in the supine position, measurements were made in the alternate mode, 1200 sweep, 11.7 rates, and click stimulus. Stimulus intensities used were 60 dBnHL, 40 dBnHL, 20 dBnHL, and 10 dBnHL. The amplitudes of the I./III./V. waves, the latencies of the I./III./V. waves and the latencies of the I- III/I-V/III-V interpeak were recorded.

During DPOAE measurements, the frequency density within the stimulus was determined as L1 (65 dB-SPL) for frequency f1 and L2 (55 dB-SPL) for frequency f2. The DPOAE results were recorded twice for each frequency, 1000, 1500, 2000, 3000, 4000, 6000, and 8000 Hz. In the DPOAE results, the "signal-to-noise ratio" (SNR) values determined for each frequency are read from the table generated by the test system.

Venous blood samples were collected for biochemical analysis without ingestion of drugs and after at least 10 hours of fasting. Biochemical analyzes were performed at the Central Biochemical Laboratory of our hospital NEU Meram Faculty of Medicine. Analyzes were performed using the oxidase-based technique with a modular system from Roche and Hitachi (Mannheim, Germany).

Statistical Analysis

Windows version 12.0 (SPSS Inc. Chicago/Illinois/USA) was used to analyse clinical and experimental data. Descriptive statistics were determined for each variable individually. Numeric or categorical variables were expressed as mean ± standard deviation and number per cent. Whether or not the data were normally distributed was examined using the Shapiro-Wilk test. Parametric statistics (t-test for independent samples) and nonparametric statistics (Mann-Whitney U test) were used for continuous variables. Fisher's Exact and Chi-square tests were used to compare categorical data between independent groups. A p - value of < 0.05 was considered statistically significant.

Table 1. Demographic, clinic and biochemical features of the patients with FD and healthy subjects.

Parameters	Patients with Fabry disease (n: 16)	Healthy subjects (n: 16)	*P* value
Gender (F/M)	8/8	5/11	0.280
Age (years)	33.5 ± 15.4	33.6 ± 6.3	0.976
eGFR (mL/min)	108.3 ± 49.9	103.9 ± 13.3	0.736
Glucose (mg/dL)	89.3 ± 6.3	91 ± 8.3	0.530
Urea (mg/dL)	29.6 ± 18.1	27.1 ± 7.3	0.509
Creatinine (mg/dL)	1.2 ± 1.9	0.8 ± 0.1	0.203
Sodium (mmol/L)	139.3 ± 1.8	139.1 ± 1.8	0.703
Potassium (mmol/L)	4.6 ± 0.4	4.3 ± 0.3	0.029
Total protein (g/L)	68.9 ± 3.8	72.4 ± 3	0.008
Albumin (g/L)	42.9 ± 4.1	46.7 ± 2.8	0.005
AST (U/L)	16.2 ± 3.5	20.9 ± 12.1	0.749
ALT (U/L)	13.8 ± 7.1	28.1 ± 20	0.001
CRP (mg/dL)	2.5 ± 3.9	3.4 ± 3.6	0.118
Protein/creatinine ratio in spot urine (mg/dL)	741.1 ± 1329	88.1 ± 38.6	< 0.001
White blood cell count (10^3/uL)	7.4 ± 1.3	8.3 ± 1.6	0.100
Neutrophil count (10^3/uL)	4.3 ± 1.1	4.4 ± 1.2	0.755
Lymphocyte count (10^3/uL)	2.4 ± 0.6	2.9 ± 0.6	0.033
Hemoglobin count (g/dL)	13.6 ± 1.3	14.4 ± 1.5	0.173
Platelet count (10^3/uL)	256.6 ± 58.3	270.7 ± 66.3	0.523

RESULTS

Table 1 shows the demographic data, clinical characteristics, and biochemical results of 16 patients with FD and 16 healthy control subjects. When the patients and healthy subjects were evaluated, it was found that there were no significant differences concerning the following variables: sex, age, serum levels of glucose, creatinine, sodium, CRP, haemoglobin, and platelet count. In addition, serum levels of total protein, albumin, alanine aminotransferase (ALT) and lymphocyte count were higher in the control group ($p = 0.008$, $p = 0.005$, $p = 0.001$ and p = 0.033, respectively). Serum potassium levels and protein/creatinine ratio were significantly higher in patients with FD than in control subjects ($p = 0.029$ and $p < 0.001$, respectively) (Table 1).

After the diagnosis of FD in 4 patients, 12 more affected family members were identified through family screening. The pedigree analysis provided an early diagnosis for two male relatives (nephews) of a male patient and four male relatives (2 sons and two nephews) of the other male patient. The diagnosis was made in 3 female relatives of a female patient (1 daughter, two nieces) and three relatives (2 daughters and a niece) of the other female patient. The mean duration of diagnosis was 67.69 ± 13.29 months, and the mean duration of treatment was 62.44 ± 15.21 months in patients with FD (Table 2). Nine patients were using agalsidase alfa, and seven were using agalsidase beta. In addition, the patients' enzyme levels and lyso Gb-3 levels were given in Table 2.

When the hearing functions of the participants were evaluated, it was found that the rate of hearing loss was higher in the patients with FD than in the healthy control group ($p = 0.033$). According to the results of PTA, conductive hearing loss was detected in 4 (25%) of the FD patients, while it was not detected in the control group. The mean value of hearing thresholds obtained with PTA in the patients with FD and the control groups was within the normal range in the bone and airway for both ears. However, when the frequencies of 500-4,000 Hz were assessed, the bone pathway hearing threshold in both ears was higher in the FD patients than in the healthy control group ($p = 0.014$ and $p = 0.014$, respectively) (Table 3).

When we compared the otoacoustic distortion product measurements of the FD patients and the control group, the dB value measured at 2.8 kHz was lower in the patient group ($p = 0.018$). When we compared the ABR measurements, the right ear's 3-5 interpeak latency at 60 dB was lower in the patients with FD (1.8 ± 0.3 vs 2 ± 0.2 ms, $p = 0.033$).

When patients were divided into groups after agalsidase treatment, there were no significant differences in sex, age, serum glucose, serum creatinine, sodium, potassium, C-reactive protein, lymphocyte count, and platelet count between the treated and untreated groups; only the spot urine protein/creatinine ratio was higher in the treated group ($p = 0.039$). Hearing thresholds determined with PTA in the treated and untreated patients were within the normal bone and airway range at all frequencies between 250-8,000 Hz in both ears. No significant difference

Table 2. Diagnosis, treatment dates and enzyme levels of patients with Fabry disease.

No	Gender	Age (years)	Dignosis date	FD duration (months)	Treatment date	Treatment duration (month)	Enzyme level	Lyso Gb-3	Treatment
1	Female	19	01.01.2017	72	01.01.2018	60	2.5	5.2	Agalsidase alfa
2	Male	48	01.01.2017	72	01.01.2018	60	0.2	4.6	Agalsidase alfa
3	Female	21	01.03.2017	69	01.06.2017	67	0.8	1.8	Agalsidase alfa
4	Female	33	01.06.2019	43	17.02.2020	35	2.1	4.2	Agalsidase beta
5	Male	37	11.11.2015	86	01.01.2016	84	0.9	39.3	Agalsidase beta
6	Male	39	23.11.2015	86	01.01.2016	84	1.4	27.5	Agalsidase beta
7	Male	47	08.06.2016	79	01.10.2016	75	0.2	1.7	Agalsidase beta
8	Female	36	11.01.2019	48	01.11.2019	38	2.0	7.9	Agalsidase beta
9	Male	25	18.10.2016	74	23.02.2017	71	1.2	60.8	Agalsidase alfa
10	Female	66	03.01.2017	71	23.02.2017	71	2.4	11.5	Agalsidase alfa
11	Male	38	01.02.2017	70	23.02.2017	71	1.2	23.3	Agalsidase beta
12	Female	43	11.04.2017	68	03.08.2017	65	2.3	14.7	Agalsidase alfa
13	Female	19	04.03.2019	45	01.09.2019	40	2.5	5.2	Agalsidase alfa
14	Male	48	01.03.2018	58	01.12.2018	49	0.2	4.6	Agalsidase alfa
15	Female	21	09.10.2017	63	01.03.2018	58	0.8	1.8	Agalsidase alfa
16	Female	33	19.06.2016	79	17.02.2017	71	2.1	4.2	Agalsidase beta

Table 3. Comparison of audiometry findings of the patients with FD and healthy subjects.

Parameters	Patients with Fabry disease (n: 16)	Healthy subjects (n: 16)	*P* value
Right ear 500-4000 Hz (air)	9.1 ± 4.8	6.6 ± 1.7	0.253
Right ear 4000-8000 Hz (air)	12.9 ± 8.7	8.4 ± 1.8	0.474
Right ear 500-4000 Hz (bone)	6.5 ± 3.8	3.8 ± 2.1	0.014
Left ear 500-4000 Hz (air)	8.4 ± 3.7	6.5 ± 1.7	0.200
Left ear 4000-8000 Hz (air)	12.3 ± 7.1	8.3 ± 1.7	0.361
Left ear 500-4000 Hz (bone)	6.3 ± 3.4	3.8 ± 2.1	0.014
Hearing loss n (%)	4 (25)	0	0.033

was found between the two groups.

When the measurements of the otoacoustic distortion product of the groups were evaluated, it was found that the dB value at the right ear SNR 1.4 and 2.8 kHz and at the left ear SNR 1.0, 1.4, 2.0, and 2.8 kHz was significantly higher in the untreated patient group ($p = 0.027$, $p = 0.050$; $p = 0.014$, $p = 0.022$, $p = 0.08$, and $p = 0.029$, respectively) (Table 4). When the ABR measurements were evaluated between the groups, it was found that there was no statistical difference.

DISCUSSION

As a result of the study, we came to three important conclusions. First, proteinuria was significantly increased in FD patients compared with the control group. Second, the proportion of patients with hearing loss was higher in FD patients. Third, the average hearing threshold of patients with FD was higher than that of the healthy group at the frequencies of 500-4,000 Hz in the bone tract for both ears.

FD is a genetic storage disease that plays a role in chronic kidney disease but can be treated. Renal findings occur in at least 20% of females and about 50% of male patients.[9] The primary renal finding is usually proteinuria.[10] In a study by Turkmen *et al*.[11], the incidence of proteinuria in 30 patients with FD was 23.3%. According to the literature, the protein-to-creatinine ratio in our study's puncture urine was higher in patients with FD than in the control group. When we divided the patients with and without treatment into groups, the ratio of protein to creatinine detected in the puncturing was higher in the treatment group. This result may be attributed to treated patients having more severe diseases and being more likely to develop organ damage.

The effects of FD on hearing have also been described in the last 15 years. Several studies have reported that progressive sensorineural and episodic hearing loss is more common than the average population, especially at high frequencies.[12,13] Sergi *et al*.14

Table 4. Autoacoustic emission findings of treated and nontreated FD patients with agalsidase.

Parameters	FD patients with treatment (n: 9)	FD patients without treatment (n: 7)	*P* value
Right ear SNR 1.0 kHz	4.6 ± 7.8	8.6 ± 8.3	0.339
Right ear SNR 1.4 kHz	5.9 ± 6.1	13 ± 5.2	0.027
Right ear SNR 2.0 kHz	2.4 ± 5.8	8.2 ± 6.1	0.074
Right ear SNR 2.8 kHz	-7.4 ± 13.2	2.0 ± 9.2	0.050
Right ear SNR 4.0 kHz	0.3 ± 8.2	0.7 ± 8.1	0.791
Right ear SNR 6.0 kHz	-6.0 ± 12.9	-2.7 ± 9.8	0.588
Right ear SNR 8.0 kHz	-15.1 ± 6.9	-13.7 ± 9.7	0.740
Left ear SNR 1.0 kHz	1.1 ± 9.2	12 ± 4.8	0.014
Left ear SNR 1.4 kHz	6.5 ± 4.5	12.3 ± 4.3	0.022
Left ear SNR 2.0 kHz	0.6 ± 6.4	10.2 ± 5.8	0.008
Left ear SNR 2.8 kHz	-3.4 ± 7.7	5.1 ± 5.8	0.029
Left ear SNR 4.0 kHz	1.1 ± 7.6	8.2 ± 5.8	0.060
Left ear SNR 6.0 kHz	-4.4 ± 11.5	2.9 ± 10.2	0.205
Left ear SNR 8.0 kHz	-15.7 ± 8.2	-23.3 ± 6.7	0.067

investigated the involvement of the inner ear in 20 patients with FD receiving enzyme replacement therapy (ERT). This study's patients were audiologically evaluated every six months using audiometry, OAE, and ABR methods. The mean follow-up time was 51.5 months (range: 25-73). Audiometry detected a hearing loss in 18 ears (45%) (13 patients) at pretreatment evaluation. These hearing losses were reported to be sensorineural, and the site of the lesion was the cochlea, as indicated by the OAE and ABR findings. When the planned follow-up times were reached in the study, the number of ears with hearing loss increased to 21 (52.5%), but it was found that the difference was not statistically significant. The authors suggested that inner ear involvement remains stable with ERT, so treatment should be started without waiting for hearing loss to develop. In our study, the rate of patients with hearing loss was higher than in control subjects. No difference in hearing loss was found when the treated and untreated patients were examined. But a conductive hearing loss in 4 patients could not be associated with any condition. However, it was thought that impedance changes due to FD-related deposit accumulations in the sound conduction path starting from the tympanic membrane and continuing with the malleus incus stapes and their ligaments and ending in the fenestra ovale might be a factor. However, because our study was cross-sectional, it may be misleading to make a statement about the effect of ERT on hearing loss.

In addition, hearing loss due to neurological involvement in patients with FD is another reason for blaming. In a study by Koeping *et al*.[15], %74 of FD patients were found to have sensorineural hearing loss by audiometry. In the ABR evaluation of these patients, the interpeak wave latencies I-III/III-V/I-V were within the normal range. In our study, the ABR test performed to evaluate the patients' auditory pathways found that the right ear of the patients with FD was significantly lower at 60 dB than the control group with 3-5 interpeak latencies. However, the results of ABR were found to be normal in all our patients.

In a study by Bitirgen *et al*.[16], corneal sensitivity, density, and nerve fibre length were lower in FD patients than in control subjects when evaluated by corneal confocal microscopy. Although FD-associated nerve damage was directly detected by microscopy in this study, the presence of auditory nerve damage in our study could not be seen by the ABR test. This could be because the head pairs were affected by FD at different rates or because a method that assessed electrical activity, such as the ABR test, was inadequate. Studies are needed to evaluate more patients and use other ways, such as autopsy studies.

Another question that needs to be addressed regarding hearing loss in patients with FD is whether it is possible to halt or even reverse hearing loss with treatment. To investigate this question, Palla *et al*.[17] audiometrically assessed the hearing of 47 patients before starting ERT and 60 months after treatment. The authors, who found no difference between the two evaluations, claimed that although the hearing loss was not reversed by ERT, at least hearing functions were stabilized. One of the major shortcomings of our study is that the periods before and after treatment were not evaluated to examine the effect of ERT on hearing loss.

CONCLUSIONS

As a result, we found that the hearing loss and hearing threshold rates were higher in FD patients than in the healthy group. Although the effects of pathogenesis and enzyme replacement therapy are not yet fully known, hearing screening should be systematically performed in these patients and included in this screening in asymptomatic patientsWe believe that possible hearing loss can cause a severe deterioration in the quality of life, even if it does not cause life-threatening situations, and that adverse effects on quality of life can be prevented by early diagnosis/treatment.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding Sources

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Necmettin Erbakan University (NEU) (Faculty of Medicine, Konya, Turkey). (Decision number: 2018/1179, date: 19.01.2018).

Authors' Contribution

Study Conception: FY, MAD, KT; Study Design:

FY, MAD, IB, KT; Supervision: FY, CKY, HO, YO, IB; Literature Review: FY, CKY, MAD, HO, YO; Critical Review: MAD, IB, KT; Data Collection and/or Processing: FY, CKY, MAD, HO, YO; Statistical Analysis and/or Data Interpretation: FY, IB, YO; Manuscript preparing: FY, CKY, MAD, KT. Oto-rhino-larygologic examination and Hearing functions and auditory pathways: MAD.

REFERENCES

1. Alroy J, Sabnis S, Kopp JB. Renal pathology in Fabry disease. J Am Soc Nephrol. 2002 Jun;13(Suppl 2):S134-8. doi: 10.1097/01.ASN.0000016684.07368.75. Alroy J, Sabnis S, Kopp JB. Renal pathology in Fabry disease. J Am Soc Nephrol. 2002 Jun;13 Suppl 2:S134-8.

2. Arends M, Wanner C, Hughes D, Mehta A, Oder D, Watkinson OT, Elliott PM, Linthorst GE, Wijburg FA, Biegstraaten M, Hollak CE. Characterization of Classical and Nonclassical Fabry Disease: A Multicenter Study. J Am Soc Nephrol. 2017 May;28(5):1631-41. doi: 10.1681/ASN.2016090964.

3. Curiati MA, Aranda CS, Kyosen SO, Varela P. The challenge of diagnosis and indication for treatment in Fabry disease. J Inborn Errors Metab Screen. 2017;5:1-7. doi: 10.1177/2326409816685735.

4. Hsu TR, Niu DM. Fabry disease: Review and experience during newborn screening. Trends Cardiovasc Med. 2018 May;28(4):274-281. doi: 10.1016/j.tcm.2017.10.001.

5. Calderón Sandubete EJ, Briones Pérez de la Blanca E, Alonso-Ortiz Del Río C, Santamaría Olmo R, López Mendoza M, Barcos Martínez M, Márquez Infante C, Marín-León I; en nombre del Grupo Guía Fabry. Spanish multidisciplinary clinical practice guidelines for Anderson-Fabry Disease in adults. I. Method and recommendations. Rev Clin Esp (Barc). 2019 May;219(4):200-207. English, Spanish. doi: 10.1016/j.rce.2018.09.017.

6. Lidove O, Kaminsky P, Hachulla E, Leguy-Seguin V, Lavigne C, Marie I, Maillot F, Serratrice C, Masseau A, Chérin P, Cabane J, Noel E; FIMeD investigators. Fabry disease 'The New Great Imposter': results of the French Observatoire in Internal Medicine Departments (FIMeD). Clin Genet. 2012 Jun;81(6):571-7. doi: 10.1111/j.1399-0004.2011.01718.x.

7. Laney DA, Bennett RL, Clarke V, Fox A, Hopkin RJ, Johnson J, O'Rourke E, Sims K, Walter G. Fabry disease practice guidelines: recommendations of the National Society of Genetic Counselors. J Genet Couns. 2013 Oct;22(5):555-64. doi: 10.1007/s10897-013-9613-3.

8. Spada M, Pagliardini S, Yasuda M, Tukel T, Thiagarajan G, Sakuraba H, Ponzone A, Desnick RJ. High incidence of later-onset fabry disease revealed by newborn screening. Am J Hum Genet. 2006 Jul;79(1):31-40. doi: 10.1086/504601.

9. Wilcox WR, Oliveira JP, Hopkin RJ, Ortiz A, Banikazemi M, Feldt-Rasmussen U, Sims K, Waldek S, Pastores GM, Lee P, Eng CM, Marodi L, Stanford KE, Breunig F, Wanner C, Warnock DG, Lemay RM, Germain DP; Fabry Registry. Females with Fabry disease frequently have major organ involvement: lessons from the Fabry Registry. Mol Genet Metab. 2008 Feb;93(2):112-28. doi: 10.1016/j.ymgme.2007.09.013.

10. Oruç A, Yildiz A, Akgur S, Unsal O, Aydın MF, Ersoy A, Yavuz M, Dilek K, Gullulu M. Screening for Fabry disease in patients who underwent renal biopsy and identification of a novel mutation. Turkish journal of nephrology. 2021 Apr;30(2):165-70. doi: 10.5152/turkjnephrol.2021.4709.

11. Turkmen K, Guclu A, Sahin G, Kocyigit I, Demirtas L, Erdur FM, Sengül E, Ozkan O, Emre H, Turgut F, Unal H, Karaman M, Acıkel C, Esen H, Balli E, Bıtırgen G, Tonbul HZ, Yılmaz MI, Ortiz A. The prevalence of Fabry disease in patients with chronic kidney disease in Turkey: The TURKFAB study. Kidney Blood Press Res. 2016;41(6):1016-24. doi: 10.1159/000452605.

12. Germain DP, Avan P, Chassaing A, Bonfils P. Patients affected with Fabry disease have an increased incidence of progressive hearing loss and sudden deafness: an investigation of twenty-two hemizygous male patients. BMC Med Genet. 2002 Oct 11;3:10. doi: 10.1186/1471-2350-3-10.

13. Hegemann S, Hajioff D, Conti G, Beck M, Sunder-Plassmann G, Widmer U, Mehta A, Keilmann A. Hearing loss in Fabry disease: data from the Fabry Outcome Survey. Eur J Clin Invest. 2006 Sep;36(9):654-62. doi: 10.1111/j.1365-2362.2006.01702.x.

14. Sergi B, Conti G, Paludetti G; Interdisciplinary Study Group On Fabry Disease. Inner ear involvement in Anderson-Fabry disease: long-term follow-up during enzyme replacement therapy. Acta Otorhinolaryngol Ital. 2010 Apr;30(2):87-93.

15. Köping M, Shehata-Dieler W, Schneider D, Cebulla M, Oder D, Müntze J, Nordbeck P, Wanner C, Hagen R, Schraven SP. Characterization of vertigo and hearing loss in patients with Fabry disease. Or-

phanet J Rare Dis. 2018 Aug 15;13(1):137. doi: 10.1186/s13023-018-0882-7.
16. 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 Aug 16;8(1):12244. doi: 10.1038/s41598-018-30688-z.
17. Palla A, Hegemann S, Widmer U, Straumann D. Vestibular and auditory deficits in Fabry disease and their response to enzyme replacement therapy. J Neurol. 2007 Oct;254(10):1433-42. doi: 10.1007/s00415-007-0575-y.