What Is the Role of Sensorineural Hearing Loss in Fabry Disease Screening?

Original Investigation

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Abstract

Objective: Fabry disease is a rare hereditary lysosomal storage disease caused by the deficiency of alpha-galactosidase A (α-GLA). Although sensorineural hearing loss is common in Fabry disease, there are no studies in the literature that have screened a population with sensorineural hearing loss for Fabry disease. In this study, we aimed to screen a group of patients who were diagnosed with sensorineural hearing loss and underwent a hearing test for Fabry disease.

Methods: One hundred sixty eight patients who were aged 18–75 years and diagnosed with idiopathic hearing loss between July 2019 and January 2020 were included. In male patients, α-GLA enzyme activity was analyzed. Patients with low enzyme activity were identified and genetic testing was performed for mutations in the *GLA* gene. In females, only genetic testing was performed.

Results: Eighty four women and 84 men were included in the study. α-GLA enzyme activity was low in 11 of the 84 male patients (13%). One out of these 11 patients had a gene mutation for Fabry disease. Moreover, four relatives of this index patient were diagnosed with Fabry disease in family screening. GLA gene mutation was also found in one of the 84 female patients. Consequently, two (1.2%) of our 168 patients were diagnosed with Fabry disease by screening with enzyme activity and genetic testing.

Conclusion: Our study showed that screening for Fabry disease in patients with idiopathic sensorineural hearing loss without other specific findings might be a useful strategy for detecting new cases.

Keywords: Fabry disease, sensorineural hearing loss, lysosomal storage diseases, genetic testing, alpha-galactosidase

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Introduction

Fabry disease is a lysosomal storage disease caused by the deficiency of alpha-galactosidase A (α-GLA) and shows X-linked transition (1). The findings usually begin to present in childhood. If untreated, often life-threatening complications develop when individuals reach their middle age (2). The incidence of Fabry disease is between 1:40,000 and 1:117,000 worldwide (3). However, since the findings of Fabry disease are non-specific, it is thought that some of the cases cannot be detected during the individuals' lifetime (1). Currently, neonatal screening programs for Fabry disease are being carried out in some countries, and there is a higher prevalence between 1:1,368 and 1:8,882

in these countries (4-7). These findings reveal that Fabry disease is more common than previously reported (8). That the disease has an X-linked transition and consanguineous marriages are frequent in Turkey suggests that Fabry disease can be more commonly detected in closed communities in which kinship marriages are common.

As well as many complications such as cardiomyopathy, hypertension, arrhythmia, proteinuria, renal failure, and stroke, Fabry disease causes hearing-related conditions. Tinnitus is usually the first auditory symptom and presents in approximately 27–38% of the patients (9). Many patients develop progressive sensorineural hearing loss, especially in adulthood. In a study of 68 Fabry disease patients, sensorineural hearing loss was detected in 58.8%, in whom the severity of sensorineural hearing loss and the severity of renal and cardiac functions were parallel. In these patients, hearing loss was observed as asymmetrical, starting unilaterally and then affecting the contralateral side (10).

Studies have been conducted on the incidence of Fabry disease in patients who had idiopathic clinical findings (end-stage renal failure, hypertrophic cardiomyopathy, stroke) (11-16). As a result of these studies, the incidence of Fabry disease was found to be more common in this group of patients than in the general population, hence it was concluded that screening for Fabry disease would be beneficial in similar clinical cases.

In our study, Fabry disease was screened in patients with idiopathic sensorineural hearing loss. It aimed to create a new screening strategy for this disease in which complications can be prevented with early treatment after diagnosis.

Methods

Patients who underwent audiometry as part of the routine practice at the otorhinolaryngology department between July 2019 and January 2020, and were found to have sensorineural hearing loss without a known etiology in otorhinolaryngologic examination were included in the study. Patients younger than 18 years, patients with known Fabry disease, and patients whose cause of sensorineural hearing loss could be explained by any other factor (trauma, drug use, infection, systemic diseases) were excluded. An a priori power analysis was done to determine the number of patients in the study.

An Otometrics Madsen Astera 2 (Natus Medical, Taastrup, Denmark) device was used for pure tone audiometry. World Health Organization's grades of hearing impairment were used for the classification of hearing loss (17).

In female patients, first Fabry gene mutation was studied, and in male patients, α-GLA enzyme activity was studied first by taking dry blood samples. The presence of Fabry gene mutation was also investigated later in male patients who had low enzyme activity (<2.50 nmol/mL/hours). The reason for examining genetic mutations without measuring the enzyme level in women is that this disorder is caused by mutations in the gene located on the X chromosome. Because of its X-linked inheritance pattern, males with a single copy of the mutated gene typically exhibit symptoms of the disease, while females (who have two X chromosomes) might be carriers or, in some cases, exhibit milder symptoms due to the presence of a normal copy of the gene on the other X chromosome (1). Family screening was also done for the patients diagnosed with Fabry disease. Samples required for measuring α-GLA enzyme activity and determining GLA gene mutation were prepared by 5 milliliters of blood samples taken from the patients and dropping them onto dry blood filter paper simultaneously The dry blood sample filter papers were delivered to the laboratory on the same day where they were examined by fluorimetric methods. The National Center for Biotechnology Information Genomic reference sequence: NG_007119.1, NM_000169.2 was used as the reference sequence for GLA gene mutations.

As a result of the tests, patients whose hearing loss etiology had been linked only to Fabry disease were proportioned to the total study population.

Electrocardiography, echocardiography, spot urine protein/creatinine ratio, and eye and skin examinations were done to detect other organ involvements in patients diagnosed with Fabry disease.

The study was approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (decision no: I1-08-19, date: 25.06.2019) and conducted in line with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Statistical Analysis

Statistical analyses were done using IBM SPSS Statistics for Windows (IBM Corp, Version 22.0). The Kolmogorov–Smirnov test was used to assess the normality of continuous data. Categorical variables were presented as numbers and percentages (%). Continuous data were displayed as mean ± standard deviation for normally distributed variables and median (minimum-maximum) for non-normally distributed variables. The chi-square test was used to compare the percentages of hearing loss and the severity levels between genders.

Results

Of the total 168 patients included in the study, 84 were female and 84 were male. Patient characteristics are summarized in Table 1.

α-GLA activity was found below 2.50 nmol/mL/hour in 11 (8.4%) of the 84 male patients. When the Fabry gene

Table 1. Patients' ages and sensorineural hearing loss characteristics

	Women (n=84)	Male (n=84)	Total (n=168)
Age	56.3±12.6	55.0±14.0	55.6±13.3
The beginning of the hearing loss			
Sudden	11 (13%)	16 (19%)	27 (16%)
Quiet	73 (87%)	68 (81%)	141 (84%)
Hearing loss involvement			
Bilateral	64 (76%)	74 (88%)	138 (82%)
Unilateral	20 (24%)	10 (12%)	30 (18%)
Hearing loss severity			
Mild	36 (43%)	36 (43%)	72 (43%)
Moderate	30 (36%)	31 (37%)	61 (37%)
Severe	18 (21%)	17 (20%)	35 (20%)
Tinnitus	39 (46%)	46 (54%)	85 (50%)

mutation was studied in these patients, only one patient (Index case 1) had a mutation that was proven to cause Fabry disease. The mutation detected in this patient was stated as c.1010T> C(p.F337S) hemizygote.

One out of the 84 female patients had one of the mutations proven to cause Fabry disease. The mutation detected in this patient (Index case-2) was identified as c.937G> T(p. D313Y) heterozygous. As a result, Fabry disease was found in two (1.2%) (2/168) of all patients included in the study.

The study design and the results obtained are given in Figure 1.

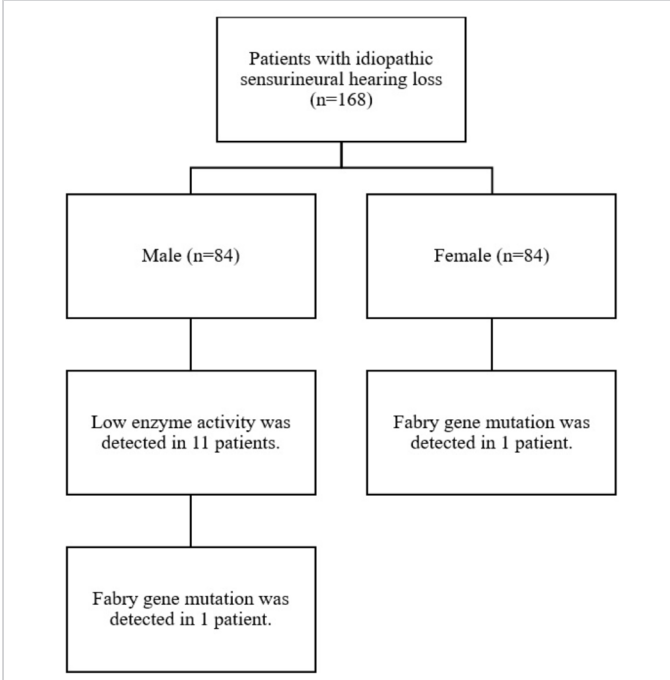

Figure 1. Study design and results obtained

Index Case-1

The only male patient with a gene mutation associated with Fabry disease was 61 years old. The patient was on follow-up for chronic kidney disease since he was in his 30s. The etiological cause of the patient's chronic kidney failure could not be determined in that period and was accepted as idiopathic. The patient was started on hemodialysis in 2009. The patient's proteinuria level could not be determined due to his anuric state.

In the previous and present echocardiograms of the patient who described intermittent effort dyspnea during the follow-up period for chronic renal failure, progressive myocardial hypertrophy was found, although the ejection fractions were in the range of 40–45%. The patient whose myocardial hypertrophy etiology could not be found was diagnosed with idiopathic hypertrophic subaortic stenosis. The patient was diagnosed with atrial fibrillation a few years after the beginning of hemodialysis treatment. With complaints of dizziness after a routine hemodialysis session in December 2018, a full atrioventricular block was detected and a permanent pacemaker was placed. The patient's ejection fraction was 45% in his echocardiography taken at that time, and the septum was extremely hypertrophic.

After the diagnosis of Fabry disease, the patient's echocardiography revealed large atrium sizes, slightly thick mitral valves, hypokinetic interventricular septum, akinetic inferior and posterior walls, biventricular hypertrophy, and global longitudinal strain as 3.1%. All these findings supported an infiltrative cardiac involvement.

In the detailed examination of the patient for further organ involvements associated with Fabry disease, no skin findings like angiokeratoma or ophthalmologic pathology were observed. He also did not experience frequent extremity pain or periodic pain crises. He had no history of cerebrovascular accidents.

The patient who had impaired hearing in his late 40s had undergone an audiometric examination, which was reported

as mild conductive hearing loss and diagnosed as idiopathic. The audiometric examination done in our study showed mild bilateral sensorineural hearing loss. Because it was decided that the existing renal and cardiac involvements would not benefit from enzyme replacement therapy, enzyme replacement therapy was not started.

After the diagnosis of Fabry disease, family screening was made for the patient's family. The disease was found in the patient's uncle aged 74 years, and two male and one female cousins aged 38, 35, and 34 years, respectively. The uncle had proteinuria, stage three chronic kidney disease, and heart failure. Enzyme therapy was not initiated due to his age and the progression of the disease. The patient's two male cousins had asymptomatic proteinuria and pain crises. The female cousin was asymptomatic, her cardiac and renal examinations were normal. The two male cousins were started on enzyme therapy. There were consanguineous marriages between the patient's mother and father and between the mothers and fathers of their cousins who had the disease. The mother of the patient had died of renal failure at a young age. Also, although the cause was not fully understood, his grandmother had died at an early age. The patient's family pedigree is given in Figure 2.

Index Case-2

This patient was a 54-year-old female. She was included in the study due to the detection of mild unilateral sensorineural hearing loss. She had no known history of illness nor was she taking any medication. There was no family history of renal failure, heart failure, or cerebrovascular accident. Her brother had hearing loss at the age of 30. Her renal functions and echocardiography were normal. No proteinuria was detected in the urine. No pathologies were detected in the eye and skin examinations. There were no symptoms of painful crisis, abdominal pain, or decreased sweating. Mild sensorineural hearing loss was the only finding associated with Fabry disease in the patient. The patient's family could not participate in the Fabry Disease screening due to the coronavirus disease-2019 pandemic outbreak.

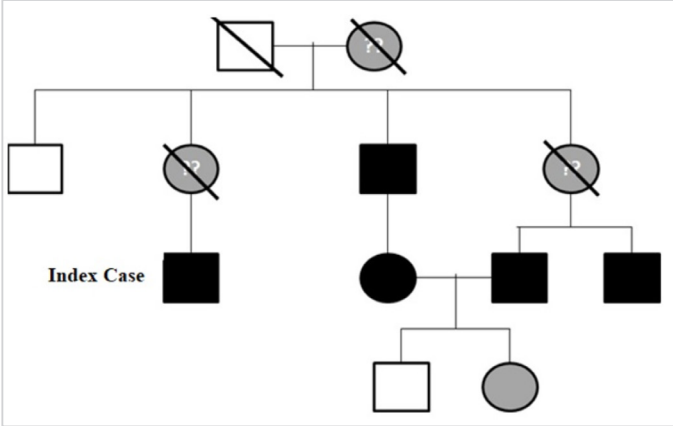

Figure 2. Family pedigree of the male patient diagnosed with Fabry disease at the end of the study

Discussion

Presently, there are no exact data for Fabry disease incidence in Turkey. In this study, Fabry disease was found in 1.2% (2/168) of our study cohort. Although two of the study patients were diagnosed, four more were diagnosed with Fabry disease in family screenings. Although Fabry disease is evaluated in the rare group of metabolic diseases, we believe that this frequency might be significantly higher since our study was conducted with a specific group of patients and in a country where consanguineous marriage is common. To obtain healthier data, multi-center studies that support these findings should be conducted with more patients. Achieving similar results in a larger population would guide the development of Fabry disease screening programs.

As mentioned above, enzyme replacement therapy was not given to the male patient, but the two family members diagnosed in family screening had early diagnoses of renal and/or cardiac involvement, therefore decision was to start them on enzyme replacement therapy. This screening provided the possibility of protecting family members from morbidity caused by Fabry disease as well as the possibility for early diagnosis in the next generations. Previous studies have proved that if enzyme treatment was started by detecting Fabry disease at that time, it may prevent these complications or delayed their occurrence (18-20). So, early diagnosis and treatment of Fabry disease give a chance to prevent disease complications. It makes Fabry disease a disease that may be suitable for screening programs.

In a 2016 study conducted in Turkey, Fabry disease was screened in 1,527 dialysis patients with idiopathic end-stage renal failure and the authors reported to have found low α-GLA activity in 130 (8.5%). In five (0.3%) of these patients, GLA gene mutation was detected, and Fabry disease diagnosis was confirmed (11). In another study conducted with 5,657 end-stage renal disease patients, 17 (0.3%) were diagnosed with Fabry disease (21). This is one of the studies that show the importance of screening for Fabry disease.

Screening studies have also been conducted on cardiac involvement, another complication of Fabry disease. In a study from Turkey which included 80 patients with idiopathic left ventricular hypertrophy, hemizygous mutations associated with Fabry disease were detected in two male patients (2.5% of the screened population) (22). In another study conducted in Japan in 2012, 738 male patients with idiopathic left ventricular hypertrophy were screened for Fabry disease and three (0.4% of the screened patients) were diagnosed (12).

Although sensorineural hearing loss is a common condition in Fabry patients and frequently followed-up as idiopathic,

no screening studies have been reported in this patient group to date. In a 2002 study, Germain et al. (23) investigated the cochlear functions of 22 homozygous male patients with classical Fabry disease and found the prevalence of hearing loss as 54.5%.

In our male patient that was diagnosed with Fabry disease, the absence of characteristic clinical signs of the disease such as angiokeratoma, cornea verticillata, limb pains**,** and acroparesthesia in the presence of sensorineural hearing loss- indicates that the disease has a heterogeneous clinical picture. The absence of any other clinical findings suggests that the presence of idiopathic sensorineural hearing loss alone should be sufficient for screening the disease.

Another noteworthy finding of our study was that although α-GLA enzyme activity was found to be low in 11 male patients, any of the gene mutations associated with Fabry disease was detected in only one patient. According to the current literature, low α-GLA enzyme activity in leukocytes has diagnostic value in male patients (24). Based on the results of our study, we can attribute the inconsistency between enzyme activity measurement and genetic sequencing results to two possibilities. Firstly, measurement of enzyme activity in peripheral leukocytes may be more accurate than the measurement of a sample on dry filter paper. The second is that there may be genetic mutations that have not yet been identified for Fabry disease and therefore cannot be investigated. While there were 429 gene mutations known by 2005, today more than 900 mutations are known (25, 26). This fact also supports the second assumption.

The mutation detected in our female patient who was diagnosed with Fabry disease and did not have clinical findings of the disease was defined as c.937G> T(p.D313Y). This mutation is related to a later-onset milder phenotype than the typical phenotype (27). c.1010T> C(p.F337S) gene mutation was detected in the male patient with the disease.

One of the limitations of our study is the lower number of patients compared to the other studies on Fabry disease screening. Prospective studies with a larger number of patients are needed. The inability to perform family screening of index case 2 due to the pandemic conditions has been another limitation in our study.

Conclusion

Given that Fabry disease was found in 1.2% (2/168) of the patients, our study showed that screening for Fabry disease is a beneficial strategy for detecting new cases in patients with idiopathic sensorineural hearing loss, as Fabry disease should be considered in the differential diagnosis in this group of patients. While one of our cases diagnosed with Fabry disease had sensorineural hearing loss, the absence of characteristic clinical findings of the disease such as angiokeratoma, corneal verticillata, limb pain, and acroparesthesia, supports the idea of using sensorineural hearing loss as the primary parameter in screening.

*The article was created from the corresponding author's thesis of internal medicine specialty.

Ethics Committee Approval: The study was approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (decision no: I1-08-19, date: 25.06.2019) and conducted in line with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.Y.K., S.Y., Concept: E.Y.K., A.G.C., S.Y., Ö.D., Design: E.Y.K., Ö.D., Data Collection and/or Processing: E.Y.K., S.Y., Ö.D., Analysis and/or Interpretation: E.Y.K., A.G.C., Literature Search: E.Y.K., A.G.C., Writing: E.Y.K., A.G.C., Ö.D.

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Main Points

- This study aimed to screen for Fabry disease in patients with idiopathic sensorineural hearing loss.
- Eighty four female and 84 male patients were included in the study. At the end of the study, a gene mutation associated with Fabry disease was detected in one female patient and one male patient.
- After the family screening, a genetic mutation associated with Fabry disease was detected in four relatives of the male patient.
- This study showed that screening of Fabry disease is a beneficial screening strategy for detecting new cases in patients with idiopathic sensorineural hearing loss and Fabry disease should be considered in the differential diagnosis in this group of patients.

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