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Original research article

Prevalence of Fabry disease in men with tinnitus and sensorineural hearing loss

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Abstract
Fabry disease (FD) is a lysosomal storage disorder caused by pathogenic mutations in the alpha-galactosidase A (AGALA) encoding gene region. This rare disease affects several organs including the cochlea-vestibular system. Tinnitus and sensorineural hearing loss (SNHL) are reported among otoneurological symptoms. Early and correct diagnosis of FD is important with a view to available therapy. The aim of the study was to screen for alpha-galactosidase deficiency in men with tinnitus/SNHL. A prospective multicentric study including consecutive patients with SNHL confirmed by tone audiometry or tinnitus evaluated (10/2016–8/2019). The diagnosis of AGALA deficiency was done by dry blood spot method using a threshold of 1.2 μmol/l/h. Only men aged 18–60 were included. 181 patients were subject to evaluation. SNHL was reported in 126 (70%) patients, 50 (28%) patients had unilateral, 76 (42%) patients had bilateral SNHL. Tinnitus was found in 161 (89%) patients, unilateral in 96 (53%) and bilateral in 65 (36%) patients. Suspected FD was not detected in any patient; alpha-galactosidase The AGALA values ranged 1.5–8.8 μmol/l/h, an average of 3.4 μmol/l/h. None of the 181 patients participating in the study had AGALA levels below the threshold 1.2 μmol/l/h. The occurrence of tinnitus and sensorineural hearing loss in men appears to be an irrelevant clinical sign for FD systematic screening.

Keywords: Alpha-galactosidase; Fabry disease; Screening; Sensorineural hearing loss; Tinnitus

Highlights:
- Incidence of tinnitus in men appears to be an irrelevant leading symptom for the screening of FD.
- Incidence of sensorineural hearing loss in men appears to be an irrelevant leading symptom for the screening of FD.
- Screening by alpha-galactosidase collection in patients with tinnitus or sensorineural hearing loss is not considered reasonable.

Introduction

Fabry disease (FD) is a rare genetic X-linked lysosomal storage disease caused by mutations within the gene encoding alfa-galactosidase A (AGALA). Despite the X-lined inheritance, heterozygous females may also be affected. Hemizygous males are usually affected more severely with an earlier manifestation of symptoms (Golan et al., 2015; Köping et al., 2018). The deficiency of the AGALA enzyme leads to intralysosomal accumulation of globotriaosylceramide (Gb3) in the cells of various tissues. This results in damage to the kidneys, heart and nervous system (Golan et al., 2015; Rekova et al., 2018). First symptoms caused by peripheral nerve involvement may be experienced in childhood. Depending on phenotype expression, myocardial replacement fibrosis, hypertrophic cardiomyopathy and/or renal failure may already occur in early adulthood. The central nervous system and the gastrointestinal tract may also be affected (Keilmann et al., 2006; MacDermot et al., 2001; Rekova et al., 2018). Moreover, the disease involves the

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cochleovestibular system causing a progressive hearing loss, tinnitus, and vertigo (Hughes et al., 1996; Köping et al., 2018; Rekova et al., 2018; Schachern et al., 1989). Tinnitus is the perception of sound within one or both ears of a patient or in the head when no external sound is present. It is often associated with impaired hearing. Tinnitus is often described as ringing, hissing, chirping, screeching or buzzing in the ears or near the head. So far, no study has shown a clear cause of subjective tinnitus, nor has any study brought about unequivocal success of any of the therapeutic modalities (Holy et al., 2016).

Early histological findings showed seropurulent effusion in the middle ear and hyperplastic mucosa, atrophy of spiral and strial ligament, and loss of outer hair cells. A Gb3 storage in spiral ganglia was not found and neither storage nor secondary damage was demonstrated in jackets, utricles or semicircular canals (Desnick et al., 2003; Friedman et al., 2000; Hughes et al., 1996; Schachern et al., 1989).

Enzyme replacement therapy (ERT) reduces the accumulation of Gb3 in endothelial cells within the kidneys and the heart and appears to slow down the disease progression rate (Golan et al., 2015; Hughes et al., 2008; Hwu et al., 2009; Lin et al., 2009; Spada et al., 2006). Recently a small molecule migalastat was approved for treatment of patients with amenable mutations. At least two studies have shown a positive effect of ERT on stabilizing the hearing loss and improving the vestibular function (Hajioff et al., 2003b; Sergi et al., 2010). The effect of the new FD therapy with molecular chaperone – migalastat on hearing is not yet known (Golan et al., 2015; Rekova et al., 2018). An early initiation of the treatment is crucial, since irreversible changes affecting the heart, kidney and brain are no more responsive to any treatment measures. Therefore, a timely diagnosis appears of utmost importance.

In men, the diagnosis is confirmed by measurements of AGALA levels in plasma, leukocytes or fibroblasts. In case of pathologic enzyme activity, additional genetic testing would be recommended. The levels constantly very low even in milder later-onset variants. Of note, dried blood spot sampling may be used facilitating larger screening programs (Golan et al., 2015; Rekova et al., 2018). Diagnosis is easy in males, with dosage of alpha-galactosidase A enzyme activity into leukocytes, but more difficult in females who can express normal residual activity (Michaud et al., 2020). In females, AGALA levels are usually higher or even normal and the diagnosis requires the use of other biomarkers such as lyso-Gb3 and confirmation by gene sequencing (Desnick et al., 2003; Friedman et al., 2000).

Fabry disease is a rare disease. As of December 12, 2020, a total of 231 patients, 88 men and 143 women are registered in the Fabry Disease Center in the Czech Republic (data from prof. Linhart/ Co-author). The incidence of FD was previously estimated from 1 : 40000 to 1 : 117000 (Desnick et al., 2003; Friedman et al., 2000; Golan et al., 2015; Rekova et al., 2018), whereas recent neonatal screening programs demonstrated a much higher incidence (Hwu et al., 2009; Lin et al., 2009; Spada et al., 2006). Although neonatal screening programs are feasible, they result in identification of many variants of unknown significance or benign variants. Therefore, many studies were trying to establish the prevalence of FD in populations with organ manifestations typical for FD. These included patients with end-stage of renal disease, early stroke, unexplained left ventricular hypertrophy and/or hypertrophic cardiomyopathy and others. However, a systematic screening of the disease in patients with sensorineural hearing loss (SNHL) and/or tinnitus was never performed. Therefore, we aimed to perform such a study screening consecutive male patient with either manifestation.

Materials and methods

We performed a prospective multicentric study – three centers – approved by local ethics committees; in ENT departments of three university hospitals: Department of Otorhinolaryngology and Maxillofacial Surgery, 3rd Faculty of Medicine, Charles University and Central Military Hospital, Prague, Czech Republic, trial registration number: 108/9-22/2016; Department of Otorhinolaryngology, 3rd Faculty of Medicine, Charles University and FNKV, Prague, Czech Republic, trial registration number: 48/0/2016; Department of Otorhinolaryngology and Head and Neck Surgery, St. Anna University Hospital, Brno, Czech Republic, trial registration number: 77V/2016. The written informed consent was obtained from all patients. The study was approved by ethics committees of all three study hospitals.

The main objective of the study was to screen male patients with tinnitus or sensorineural hearing loss (SNHL) for AGALA deficiency to diagnose FD. The screening period started in October 2016 and ended in August 2019.

We included only males aged 18–60 (mean 42.6; median 43), suffering from either tinnitus, or sensorineural hearing loss, or both. All enrolled patients underwent ENT examination, hearing test – pure tone audiometry and tinnitus masking (Clinical audiometer Orbiter 922, version 2, manufactured by Madsen electronics).

For the dried blood spot testing, blood was collected from the finger, samples were anonymized and mailed to the central laboratory (Archimed Laboratories, Vienna, Austria, prof. Streubel). The value of AGALA below 1.2 μmol/l/h was chosen as a threshold to suspect FD and proceed to gene sequencing.

Statistical analysis of data

Descriptive statistical analyses were performed with IBM SPSS Statistics (version 22.0; SPSS, IBM, Armonk, NY,USA).

Results

The alpha galactosidase A level was above the limit value of 1.2 μmol/l/h in all cases. The levels ranged between 1.5 and 8.8, with mean value was 3.4 ± 1.2 μmol/l/h, and median value was 3.2 μmol/l/h.

Pure tone audiometric tests revealed sensorineural hearing loss in 126 patients (70%), unilateral in 50 patients (28%) and bilateral in 76 (42%) patients.

The average hearing thresholds (in dB) at different frequencies of a tone audiogram are provided in Table 1.

Retrocochlear lesion was not confirmed in our cohort of 181 patients.

Tinnitus was experienced by 161 patients (89%), unilateral in 96 patients (53%), bilateral in 65 patients (36%). 226 ears were affected with tinnitus. Table 2 shows the tinnitus frequency distribution of 226 ears tested.

Table 1. Average hearing thresholds (in dB) at different frequencies

Threshold frequency	125 Hz	250 Hz	500 Hz	1000 Hz	2000 Hz	4000 Hz	8000 Hz
DX (dB)	19.06077	18.01105	18.12155	19.69613	20.46961	27.48619	35.52778
SD (standard deviation)	17.82482	17.5806	16.95768	19.51613	20.07418	21.68348	25.98612
SIN (dB)	19.28177	18.53591	18.8674	19.22652	20.69061	28.78453	37.07182
SD (standard deviation)	14.78675	15.25469	15.66007	15.41855	16.19133	21.43888	25.04974

Table 2. Tinnitus frequency distribution of 226 ears tested

Tinnitus/frequency	*n*	%
125 Hz	4	1.77
250 Hz	1	0.44
500 Hz	6	2.65
1000 Hz	1	0.44
2000 Hz	7	3.10
3000 Hz	4	1.77
4000 Hz	21	9.29
6000 Hz	43	19.03
8000 Hz	94	41.59
12500 Hz	2	0.88
Tinnitus cannot be masked	37	16.37
Tinnitus in ears/head	6	2.65

Discussion

We performed our screening study since in FD several authors described cochleovestibular disorders, including vertigo and progressive hearing loss, as well as tinnitus, in a substantially higher frequency than in the general population (Keilmann et al., 2006; Rekova et al., 2018). However, our prospective multicentric study conducted on 181 men with sensorineural hearing loss or tinnitus, the screening using dried blood spot testing for AGALA activity did not reveal a suspected Fabry disease in any of the study subjects.

Hearing loss in Fabry disease

According to Keilmann et al. (2006) in FD a slowly progressive SNHL predominates but the frequency of sudden SNHL is also more prevalent as compared to the general population. They reported that about 75% of female over 60 years of age and 85% of male over 50 years of age suffer from severe hearing loss.

MacDermot et al. (2001) found 41% of patients with hearing loss, 78% of patients with an abnormal audiogram, and 38% of patients with tinnitus in group 98 male patients with FD.

Germain (2001) found, in a group of 22 hemizygous males, an abnormal hearing in 12 patients (7 patients had sudden hearing loss and 5 patients had a progressive hearing loss), and tinnitus in 6 patients.

All cases of deafness were sensorineural and more than half of them were high frequency (Germain, 2001). A high frequency of sudden hearing loss was found also by Sergi et al. (2010).

According to Schuknecht's classification is the hearing disorder in patients with FD most closely resembles presbyacusis (Keilmann et al., 2006; Schuknecht and Gacek, 1993). Hegemann et al. (2006) analyzed data from 566 patients.

Ear-related symptoms were found in 316 patients. However, in the large international FD patient registry (Fabry Outcome Survey), the reported prevalence of sudden hearing loss was much lower (Hegemann et al., 2006; Keilmann et al., 2006). An analysis of the audiograms of the ear with the worse hearing in each patient with FD, according to the World Health Organization classification of hearing impairments, which better reflects the functional impairment in an age-independent manner, produced a different result. 84% of patients were classified as normal, 12% of patients had a mild hearing impairment and only 2% of patients had a mild or severe hearing impairment (Desnick et al., 2003; Keilmann et al., 2006).

Germain (2001) reports that SNHL was more common in older patients, while the normal hearing was most common in the younger age group of patients.

Most patients over the age of 40 had mild to severe hearing loss. Hegemann et al. (2006) reported that the hearing loss of FD patients strongly correlated with age at all frequencies.

Tinnitus in Fabry disease

Cases of a short episode of tinnitus have already been reported in the early teen years (12 to 15), with continued tinnitus of varying degrees of severity in adulthood (Germain, 2001; Hajioff et al., 2003b). Based on the data from the FD patient database, tinnitus is more common than hearing loss in younger patients. On other hand, the frequency of each symptom increases with age of patients. Unfortunately, the severity of tinnitus has not yet been documented in this database of FD patients, despite effect of tinnitus on the quality of life may be vary considerably in specific patient. Otoneurologic problems should be examined in all patients with FD, because may significantly affect quality of life. All patients should undergo a thoroughly audiological assessment, because patients with severity hearing loss could benefit from indicated of a hearing aid (Keilmann et al., 2006).

Potential mechanisms causing hearing impairment and tinnitus in FD

Hegemann et al. (2006) suggested, that the distorted vessels in the stria vascularis (probably caused by accumulation of Gb3 in the vascular epithelium) could be the main factor in FD-related hearing impairment.

On other hand, sudden hearing loss can by also related to vascular pathology, because patients may suffer from recurrent microvascular infarcts from stenosis or occlusion of small vessel caused by thickening of smooth muscle cells and endothelial cells (Hughes et al., 1996; Mattox and Lyles, 1989). In addition, hypercoagulation may be contributed to the worsening of blood supply to the inner ear in FD patients (Hughes et al., 1996; Köping et al., 2018; Rekova et al., 2018; Schachern et al., 1989).

According to the latest work of Köping et al. (2018), hearing loss at high frequencies and vertigo are common in FD

patients, and the hearing loss is caused by a cochlear lesion with no evidence of retrocochlear pathology (Hegemann et al., 2006).

Effects of enzyme replacement therapy

Preliminary results of recent studies suggest that enzyme replacement therapy (ERT) in FD could have a partial beneficial effect in patients with mild or moderate SNHL (Hajioff et al., 2003a; Keilmann et al., 2006; Rekova et al., 2018). ERT may, according to some studies, have an effect on stabilizing the hearing loss (Hajioff et al., 2003b; Sergi et al., 2010).

Study limitations

The main limitation of our study is the sample size evaluated. However, to our knowledge this is the largest sample of cases with ENT symptoms in FD was screened by using the DBS technique. Since hearing impairment and tinnitus in FD show a high prevalence, our assumption that some FD patients may perceive this manifestation as leading symptom and seek ENT advice was relevant. Similar strategy based on identification of patients with some significant symptoms related to FD were applied in the past. Many screening studies in hypertrophic cardiomyopathy, unexplained left ventricular hypertrophy, end-stage renal disease, and premature stroke were successful in finding affected individuals (Golan et al., 2015; Hegemann et al., 2006; Hughes et al., 2008; Lin et al., 2009; Rekova et al., 2018; Sergi et al., 2010).

Conclusions

Fabry disease is a rare genetic metabolic disorder in which early diagnosis and effective enzyme replacement therapy are important. Tinnitus or sensorineural hearing loss are often described as early symptoms of FD. In the prospective study, the screening alpha-galactosidase assay using dried blood spot did not detect suspected value of less than 1.2 μmol/l/h in any of the enrolled patients with tinnitus and/or hearing loss.

The incidence of tinnitus and sensorineural hearing loss in men appears to be an irrelevant leading symptom for the screening of FD. Introducing into ENT practice FD screening by alpha-galactosidase collection in patients with tinnitus or sensorineural hearing loss is not considered reasonable. In order to confirm the data and gain deeper insight into the problematics, it is necessary to perform study on a larger group of patients.

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Conflict of interests

All the authors declare that they have no conflict of interests.

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