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

Richard Holy 1, Tereza Hlozkova 2, Klara Prochazkova 3, David Kalfert 4 *, Frantiska Hybnerova 1, Denisa Ebelova 5, Berthold Streubel 6, Martin Chovanec 3, Bretislav Gal 2, Ales Linhart 5, Jaromir Astl 1

1 Charles University, Third Faculty of Medicine, Military University Hospital, Department of Otorhinolaryngology and Maxillofacial Surgery, Prague, Czech Republic
2 Masaryk University, Medical Faculty, St. Anne’s University Hospital, Department of Otorhinolaryngology and Head and Neck Surgery, Brno, Czech Republic
3 Charles University, Third Faculty of Medicine, Faculty Hospital Kralovske Vinohrady, Department of Otorhinolaryngology, Prague, Czech Republic
4 Charles University, First Faculty of Medicine, University Hospital Motol, Department of Otorhinolaryngology and Head and Neck Surgery, Prague, Czech Republic
5 Charles University, First Faculty of Medicine, General University Hospital, 2nd Department of Medicine – Department of Cardiovascular Medicine, Prague, Czech Republic
6 Medical University of Vienna, Clinical Institute for Pathology, Vienna, Austria

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 alpha-galactosidase A (AGALA). Despite the X-linked 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...
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 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.

Retrococchlear 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.
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.

### 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.

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### 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 the 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. Oto-neurologic 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 be 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; Koping et al., 2018; Rekova et al., 2018; Schachern et al., 1989).

According to the latest work of Koping 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 retrococal pathology (Hegemann et al., 2006).

**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.

**References**


Pharmagenesis.


