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Abstract

Hearing loss is a common symptom in Fabry disease, but neither its natural course nor its aetiology has been defined precisely. The aim of this study was to provide a detailed epidemiological description of hearing impairment in patients in the Fabry Outcome Survey (FOS), which is the largest available database of Fabry patients. Questionnaires were completed by 566 Fabry patients, of whom 316 reported ear-related symptoms. Pure-tone audiograms from 86 patients, performed before starting enzyme replacement therapy, were analysed and compared with age- and sex-specific normal values (International Organization for Standardization, ISO 7029). When compared to an age-matched population (ISO 7029), 74% of patients had a threshold elevated above the 95th centile in at least one tested frequency. All frequencies were affected to a similar degree. However, only 14 patients (16%) were clinically affected by hearing impairment according to the age-independent World Health Organization (WHO) classification (mean threshold at 0.5, 1 and 2 kHz worse than 25 dB). Hearing loss was sensorineural in 63 patients (73%) of whom 7 patients (8%) had also a conductive component. One patient had a purely conductive hearing loss. Episodes of sudden hearing loss seemed to occur more frequently than in the general population. Men were affected earlier and more severely than women. Hearing in Fabry disease is significantly worse than in an age-matched general population but leads to clinically relevant hearing impairment in only 16% of cases. It resembles accelerated presbycusis with an additional Fabry-specific strial-type hearing loss.
Hearing loss in Fabry disease: data from the Fabry Outcome Survey

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Abstract

Background Hearing loss is a common symptom in Fabry disease, but neither its natural course nor its aetiology has been defined precisely. The aim of this study was to provide a detailed epidemiological description of hearing impairment in patients in the Fabry Outcome Survey (FOS), which is the largest available database of Fabry patients.

Materials and methods Questionnaires were completed by 566 Fabry patients, of whom 316 reported ear-related symptoms. Pure-tone audiograms from 86 patients, performed before starting enzyme replacement therapy, were analysed and compared with age- and sex-specific normal values (International Organization for Standardization, ISO 7029).

Results When compared to an age-matched population (ISO 7029), 74% of patients had a threshold elevated above the 95th centile in at least one tested frequency. All frequencies were affected to a similar degree. However, only 14 patients (16%) were clinically affected by hearing impairment according to the age-independent World Health Organization (WHO) classification (mean threshold at 0.5, 1 and 2 kHz worse than 25 dB). Hearing loss was sensorineural in 63 patients (73%) of whom 7 patients (8%) had also a conductive component. One patient had a purely conductive hearing loss. Episodes of sudden hearing loss seemed to occur more frequently than in the general population. Men were affected earlier and more severely than women.

Conclusions Hearing in Fabry disease is significantly worse than in an age-matched general population but leads to clinically relevant hearing impairment in only 16% of cases. It resembles accelerated presbycusis with an additional Fabry-specific strial-type hearing loss.

Keywords Audiometry, epidemiology, Fabry disease, hearing impairment, hearing loss.

Introduction

Fabry disease (FD) is an X-linked lysosomal storage disease, affecting almost all organs with deposition of glycosphingolipids, mainly globotriaosylceramide (Gb3). Since the development of enzyme replacement therapy (ERT) with the deficient enzyme α-galactosidase A (α-GAL), there has been increased interest in both the pathophysiology and therapy of FD. A common and often worrying, though not life-threatening, symptom in Fabry patients is hearing loss. However, neither the natural course of hearing function in these patients nor its aetiology has been established in detail.

Histopathological findings in the temporal bone have been reported in only two patients [1]. The authors found abnormalities in the middle and inner ear that could
theoretically cause severe hearing and vestibular symptoms. They described hyperplastic squamous epithelium, mucoperiostal thickening and fibrosis with seropurulent effusion in the middle ear, atrophy of the stria vasculosa and spiral ligament, moderate loss of outer hair cells and mild cochlear hydrops in the apical turn. Spiral ganglion cells were decreased in number but otherwise normal with no signs of lipid storage. In addition they found haemorrhage in the saccule, hyperostosis filling the perilymphatic space of the semicircular canals and ballooning of Scarpa's ganglion cells with granulating nuclei as well as accumulation of Gb3. Glycosphingolipids were also seen in vascular endothelial cells, leading to markedly distorted vessels.

Epidemiological data on hearing loss in FD are rare. Besides anecdotal reports, only a few previous studies have investigated the natural course of hearing loss. MacDermot et al. described self-reported hearing loss in 23% of 60 heterozygous women [2] and in 41% of 61 hemizygous men [3]. In 23 of the male patients, audiograms were performed, of which 73% were deemed ‘abnormal’. Hearing has been investigated more specifically in three small studies of 22 [4], 14 [5] and 15 [6] patients with FD. These three groups found that high-frequency sensorineural hearing loss (SNHL) was the predominant abnormality. In addition, Germain et al. [5] and Conti and Sergi [4] found a high incidence of sudden onset or progression of hearing loss. Neither study found any evidence of retrocochlear pathology with brainstem audiometry. This is consistent with the normal appearance of ganglion cells found by Schachern et al. [1]. Hajioff et al. reported on three patients (13%) with conductive hearing loss due to middle ear effusion [6]. One small study found no hearing loss on pure-tone audiometry in six children with FD, but four had non-troublesome tinnitus [7].

The Fabry Outcome Survey (FOS) is a multi-centre study designed to collect data on Fabry patients in a systematic fashion to allow detailed description of functional impairments and to assess the effect of ERT on affected organ systems. The present study set out to use the pre-treatment data in FOS, which is the largest database on patients with FD, to produce a detailed epidemiological description of hearing function in affected patients.

Materials and methods

FOS database

Sixty collaborating centres from 11 countries contributed to the database (Germany, 23%; UK, 14%; Czech Republic, 11%; Switzerland, 10%; Italy, 9%; Spain, 8%; France, 7%; Belgium, 6%; Norway, 5%; Sweden, 4%; Austria, 3%). All of them are university hospitals or other tertiary referral centres for audiological patients. Medical histories were taken by FOS investigators using a standardized questionnaire. Patients were asked whether they had experienced subjective hearing loss, sudden hearing loss, vertigo or tinnitus. Data were depersonalized and entered into an internet-based database. The Ethics Committee or Institutional Review Board of all participating centres approved FOS and all patients gave written informed consent. The FOS database and its properties have been described elsewhere [8].

As of November 2004, 638 patients with FD were included in the database. The diagnosis was confirmed in all patients by enzyme assay or DNA analysis. A medical history, based on the questionnaire, was available for 566 patients (267 females [47%], mean age 39 years, range 2–76 years, and 299 males [53%], mean age 34 years, range 1–69 years). Of these, 316 (56%) reported at least one ear-related symptom in the form of hearing loss (32%), tinnitus (30%) or dizziness (30%).

Pure-tone audiograms have been obtained from 86 patients (47 females, 39 males) before starting ERT. The audiograms have been taken at 10 centres in the UK, Germany, Switzerland, Italy, France, Norway and Spain.

Hearing loss

Each patient underwent otoscopy before audiological testing. Pure-tone audiograms with air conduction thresholds at 0–25, 0–5, 1, 2, 4 and 8 kHz were performed in a quiet room by experienced audiologists, with bone conduction thresholds and masking as appropriate. All centres followed the guidelines of ISO 8253-1 (International Organization for Standardization [1989]. Acoustics – Audiometric test methods – Part 1: Basic pure tone air and bone conduction threshold audiometry). This is consistent with the normal population in ISO 7029 (International Institute for Standardization, ISO 7029 [9]). An air-bone gap was defined as an average air conduction threshold (at 0·5, 1 and 2 kHz) that was 15 dB or more above the bone conduction threshold.

Hearing thresholds were considered normal if they were better than or equal to the age-specific 95th centile of the normal population in ISO 7029 (International Institute for Standardization, ISO 7029 [9]).

To assess the clinical relevance of the audiometric data and to categorize the degree of hearing impairment, we used age-independent clinical guidelines according to the international classification of impairments, disabilities and handicaps [10]. Averages for pure-tone audiometric thresholds (PTA) at 0·5, 1 and 2 kHz were classified as normal (0–25 dB PTA), mild (26–40 dB PTA), moderate (41–55 dB PTA), moderately severe (56–70 dB PTA), severe (71–90 dB PTA) or profound (> 90 dB PTA). Our methods are comparable to those used by Germain et al. [5]. Furthermore, audiogram configurations were classified according to the criteria of Mazzoli et al. [11] as follows:

1 Low-frequency loss, ascending: the difference between the poorer low frequencies and the high frequencies exceeded 15 dB.

2 Mid-frequency ‘U’-shaped loss: the difference between the poorer mid frequencies and the better high and low frequencies exceeded 15 dB.
3 High-frequency loss, gently sloping: a 15–29 dB difference between the mean thresholds at 500 and 1000 Hz and the mean at 4 and 8 kHz.

4 High-frequency loss, steeply sloping: a 30 dB or greater difference between the mean thresholds at 500 and 1000 Hz and the mean at 4 and 8 kHz.

5 Flat: the difference between the mean thresholds at 250 and 500 Hz and at 4 and 8 kHz did not exceed 15 dB.

We excluded normal audiograms, which we defined as those in which all thresholds were no worse than 20 dB. All authors classified the audiogram shapes independently and discussed the small number in which classifications were initially discordant.

Finally, audiograms from both ears of each patient were compared and classified as bilateral symmetric, bilateral asymmetric or unilateral. The criterion for asymmetry was an interaural threshold difference of more than 15 dB in two adjacent frequencies. Conductive hearing loss was not encountered. Again, normal audiograms were excluded (based on the same criteria above).

**Sudden hearing loss**

Sudden sensorineural hearing loss (SSNHL) has been defined as a sensorineural hearing loss of 30 dB or more at three or more adjacent frequencies occurring within three days [12]. This definition could not be applied meaningfully to our database, as audiometric data around the time of the suspected SSNHL were not available. Therefore, we used the occurrence of a subjective significant hearing loss within three days as a criterion for sudden hearing loss. To distinguish this from objective SSNHL, the reported sudden hearing loss will be referred to as SHL. We compared the incidences of SHL in our Fabry population with age- and sex-matched incidences in a general population reported in a Japanese survey in 1993 [13].

**Results**

Hearing thresholds were not worse than 20 dB in any frequency bilaterally in 43 of 86 patients (50%). In the other half, hearing loss was bilateral and symmetric in 25 cases, bilateral and asymmetric in 6 cases, and unilateral in the remaining 12 cases. However, when compared with ISO 7029 hearing was normal in only 26% of patients (Fig. 1), in 30% of females and in 21% of males. The difference between sexes was not significant ($P = 0.33$). Hearing loss was most often sensorineural (63 patients, 73%). In seven of these cases (8%, 2 female, 5 male) hearing loss was mixed. A purely conductive hearing loss was found unilaterally in one female patient only. We could not determine from the database the cause or duration of these conductive hearing losses and, because of the small number of patients, we have not analysed conductive hearing losses further.

Baseline hearing thresholds in all patients (172 ears) are plotted for each frequency in Fig. 2 in relation to the 50th and 95th centiles of age- and sex-dependent hearing levels in the general population according to ISO 7029. With conductive ($n = 1$) or mixed ($n = 7$) hearing loss, bone conduction levels have been plotted; otherwise ($n = 78$) air conduction thresholds are used. We did not find a significant difference between left and right ears (paired *t*-test, $P > 0.5$). There is an obvious difference between sexes where the elevated thresholds in men are on average further from the 95th centile. There are also very few data points at or below the 50th centile especially at 8 kHz.

Compared with the ISO 7029 age-matched thresholds, only 65 of 172 ears (38%) had normal hearing levels on baseline pure-tone audiometry at all frequencies (Fig. 3). If an elevated threshold at only one frequency was accepted as normal, 55% of the patients could be classified as having normal hearing. However, 99% of all ears were above the 50th centile in at least three frequencies and 100 ears (58%) were above this median value in all frequencies. Thus, no patient had hearing consistently better than the median of a reference population. The better than average thresholds only occur at or above 1 kHz.

Looking at the relative numbers of pathological thresholds (above the 95th centile) (Fig. 4), it appears that at any of the tested frequencies about 40–50% of the patients have pathological thresholds. Lower frequencies seem to be
affected slightly more than higher frequencies but that is not statistically significant. The percentage of thresholds between the 50th and 75th centiles and between the 75th and 95th centiles increased in the Fabry population towards the higher frequencies. In general, hearing in Fabry patients resembles the age-related hearing loss in a normal population but starts earlier and progresses faster. Male patients had more severe hearing loss than female patients (Fig. 1).

Figure 2 Individual hearing thresholds of all ears of female (left-hand panels) and male (right-hand panels) patients with Fabry disease at baseline pure-tone audiometry (before the start of enzyme replacement therapy) at different frequencies. The solid lines represent the 50th centile and the dotted line the 95th centile of an age- and sex-matched general population according to the International Organization for Standardization (ISO 7029). Hearing thresholds apparently lay outside the normal range to approximately the same amount in all frequencies. In men thresholds lie clearly more often above the 95th centile and also have a greater distance to that line as compared to women. There is no evident difference between right and left ears.
Hearing impairment – age-independent

An elevated threshold in one or two frequencies might not be of clinical importance for the patient. Therefore, we evaluated the hearing impairment according to the WHO guidelines for the classification of impairments, disabilities and handicaps, which better reflects the functional impairment in an age-independent manner. This reveals a quite different picture (Fig. 5). Regarding the worse ear of each patient only, 84% of patients were classified as normal, 12% as having a mild hearing impairment and only 4% as having a moderate or severe hearing impairment (2% each).

Audiogram configuration

From the audiogram configuration for each of the 172 tested ears, 95 (55%) could be classified as normal, 42
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(24%) as flat, including 2 (1%) deaf ears, 21 (12%) as gently sloping high-frequency hearing loss and 12 (7%) as steeply sloping hearing loss. Low-frequency ascending and mid-frequency U-shaped audiograms were seen in only one ear each. Note that a sloping audiogram is the typical configuration for age-related hearing impairment and cannot necessarily be linked to FD. These results are in accordance with our analysis of individual age-related thresholds that also revealed involvement of all frequencies. The low-frequency ascending and the U-shaped audiograms, which could be suspect for cochlear hydrops, were detected in two ears only.

Sudden hearing loss

At least one episode of SHL was reported by 9 of 267 (3.4%) women (mean age 38.0 years, range 6.8–65.2 years) and by 23 of 299 (7.7%) men (mean age 37.1 years, range 14.9–54.4 years). Thus, 32 cases of SHL (5.6%) were found in the 566 patients with a complete symptom checklist. At the time of reporting, audiograms were available from 15 patients with SHL, with a mean age of 43 years (females 44 years, males 42 years), ranging between 28 and 66 years (females 28–66 years, males 33–54 years).

Six of the audiograms from the SHL patients were taken before the start of ERT. Four of these audiograms showed an asymmetry between right and left ears. As bilateral symmetric sudden hearing losses are rare (2%) [13], we...
believe that in our symmetric cases the reported episode of SHL are likely to have recovered completely or almost completely and the residual symmetrical hearing loss is the result of both age- and FD-related effects. If this assumption is correct, we estimate a rate of spontaneous recovery of 73%, which is of the same order of magnitude as seen in SSNHL in the general population.

Using data from a general population [13], the expected incidence of SHL in a normal population of the same age and sex distribution as the FOS population over the period studied is 3·1 in total, compared to the 32 that we observed in total (23 males, 9 females). This corresponds to a Standardized Incidence Ratio (observed/expected) of 10·5 (95% confidence interval: 7·2–14·8; \( P < 0·001 \)). This would correspond to an expected proportion of patients experiencing SHL of 0·96%.

**Discussion**

Using the FOS database, we have analysed 86 audiograms from a wide age range of patients with FD. This is the largest survey of hearing function in FD. Because audiometric data in the FOS registry have been collected from 10 different centres in 7 countries its validity could be criticized. These centres have not been evaluated regarding systematic audiographic differences; however, given that ISO 8253–1 guarantees a high degree of comparability we are confident that the results are valid. Comparing our data with ISO 7029, it is also valid as ISO 8253 has been applied in both populations.

A general problem in audiology is how to define ‘normal’ hearing. We have used various classifications (ISO 7029, WHO-ICIDH and audiometric configuration) throughout the literature. These gave different results, which highlight the difference between hearing loss in relation to a control population, which might be of no clinical relevance for the patient, and hearing impairment, which is age-independent and has by definition a clinical impact on the patient. Audiometric configuration is age-independent but does not contain information on clinical relevance so it cannot be compared directly with the other two classifications.

We found that hearing was worse in Fabry patients than in the general population. Hearing thresholds were consistently above the median value of an age-matched control group (ISO 7029) even where the audiograms may be classified as ‘normal’. However, in only 16% of patients, hearing loss led to a significant impairment of hearing as defined by the WHO. Hearing loss was usually slowly progressive and symmetrical in both ears, but the incidence of SHL was significantly increased in comparison with the general population. Hearing seems to be affected at all frequencies, especially in the low-frequency range, where the proportion of thresholds above the 95th centile of the general population is a little higher. However, as hearing in the normal population also declines with age, predominantly in the high frequencies, this might be the reason why Fabry patients seem relatively less impaired at higher frequencies. The equal percentages of flat (24%) audiographic configuration and high frequency loss (12% gently and 7% steeply sloping) also do not point towards a significant preference of Fabry-specific damage to high frequencies. Other factors like concomitant diseases might also be responsible for hearing loss in some of the Fabry patients. We did not analyse such factors in our study population for several reasons. First, there is no information on the distribution of such factors in the ISO 7029 population. This makes a comparison impossible. Second, we know of no reports that describe an association of FD with other diseases potentially affecting hearing. Third, Fabry-specific lesions in other organs such as the kidneys could affect hearing indirectly. Nevertheless, such an effect must also be attributed to FD and would not constitute a separate factor.

Our findings differ from previous reports by Germain et al. [5] and Hajioff et al. [6] who found a predominantly high-frequency hearing loss. With regard to results of Hajioff et al. [6] this may be due to the fact that they did not correct for non-specific age-related effects. After correction for this non-specific age-related hearing loss, our data show an additional deterioration in all frequencies that we believe to be specific to FD. This is consistent with a pathophysiologica hypothesis of a progressive degenerative process, which is supported by the findings of Schachern et al. [1]. Taking into account Schuknecht’s classification [14–16], the pattern in Fabry patients closely resembles a mixed strial and sensory type of presbyacusis. Given that the sensory type is purely age-related, the distorted vessels in the stria vascularis, presumably caused by Gb3 accumulation in the vascular epithelium, could be the main causal factor in FD-related hearing impairment. The fact that this strial type hearing loss is also age-dependent is not surprising considering that accumulation of Gb3 is progressive. Auditory brainstem response (ABR) data have not been analysed in the FOS database, as only sporadic reports are available. Nevertheless, ABR have been performed in other studies [4, 5], which found no cases of retrocochlear hearing loss. We are confident that, in at least the vast majority of Fabry patients, the origin of hearing loss is cochlear.

Cochlear hydrops seems not to play a role in FD, as we detected only two ears with, respectively, a low-frequency hearing loss and a U-shaped audiogram. Moreover, Ménière-like symptoms are neither described in previous reports nor suspected from our medical questionnaires. This is also supported by a previous study [4], showing that cochlear and vestibular involvement of the inner ear in Fabry patients do not occur in parallel, as is commonly seen in Ménière disease.

In the FOS database, 5·6% of patients reported episodes of sudden hearing loss, and men appeared to be affected 2·3 times more often than women. This is much less frequent than the 32% reported by Germain et al. [5] and the 35·7% found by Conti and Sergi [4] but is still significantly higher than the 1% expected in the general population. The risk of sudden hearing loss in our Fabry population is about 10-fold greater than in the normal population. As our data on sudden hearing loss have not been confirmed by clinical examination and audiometry around the time of the
suspected SSNHL, they must be interpreted with caution. Self-reported episodes of sudden hearing loss can for example also be caused by middle ear effusion or an earplug. Keeping that in mind we believe that our assumption is more likely to be an overestimation than an underestimation of possible SSNHL. Therefore, it seems justified to question the very high incidence of SHL in Fabry patients reported previously [4,5]. Better estimates will result from ongoing investigations within FOS.

The increased incidence of SSNHL in Fabry patients and the increased number of patients with recurrent episodes of SSNHL could be interpreted as the result of repeated microvascular infarcts from stenosis or occlusion of distorted small vessels caused by thickening of endothelial and smooth muscle cells. In addition, possible hypercoagulability in Fabry patients [17] might also contribute to a reduced blood supply to the inner ear.

In conclusion, hearing loss is very common in FD, even though a clinically significant impairment was found in a relatively small percentage of patients. Almost all hearing thresholds were worse than the general population median and roughly half were worse than the 95th centile. All frequencies, mostly in the low-frequency range, deviated significantly from the normal age-matched population. Men were affected more severely than women. Episodes of sudden hearing loss also appeared to occur more frequently than in the general population and more frequently in men than in women. Audiometric and pathological patterns resembled those of normal age-related deterioration of hearing and Fabry-specific strial-type degeneration.

A careful audiological evaluation should be part of the diagnostic assessment and follow-up of patients affected by or treated for FD.

Conflict of interest statement

The FOS database is under the independent control of the FOS European Board. Data collection and analysis in FOS are supported by Shire Human Genetic Therapies, Cambridge, MA, USA. The sponsor played no role in the interpretation of data or writing of the report. All authors received travel grants and honoraria for speaking engagements from Shire Human Genetic Therapies.

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