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ORIGINAL ARTICLE

Ear symptoms in children with Fabry disease: data from the Fabry Outcome Survey

A. Keilmann · D. Hajioff · U. Ramaswami · on behalf of the FOS Investigators

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Summary *Background*: Hearing loss and tinnitus are common symptoms in Fabry disease and increase in prevalence with age. This study aimed to provide an epidemiological description of hearing impairment and tinnitus in children with Fabry disease in the Fabry Outcome Survey (FOS), an international database to assess the natural history of Fabry disease and the efficacy of enzyme replacement therapy with agalsidase alfa. *Methods*: Signs and symptoms questionnaires were completed for 543 children with Fabry disease. Pure-tone audiograms were obtained from 101 children (53 girls, 48 boys). *Results*: On questioning, 33% of the children (n=179) reported subjective hearing impairment. However, when assessed by age-appropriate audiometry, only 19 of 101 patients (19%) had a persistent hearing loss at least one frequency. Of these, 14 had a high-frequency hearing loss, 4 a pan-frequency hearing loss, and 1 a pattern typical of noise-induced loss. Of the 101 children with audiometry, 44 complained of tinnitus. Only 2 children reported sudden hearing loss, which was not verified by audiometry. Children with tinnitus had greater disease severity scores. *Conclusions*: Hearing loss is a well-known clinical manifestation in patients with Fabry disease. It was reported in significant numbers of children in the FOS signs and symptoms questionnaire, but confirmed in only 19% by formal audiometry. The subjective hearing impairment may have been due to middle-ear effusions in many cases. Tinnitus is a well-recognized symptom in Fabry disease and can present in childhood. The presence of tinnitus correlated with overall disease severity.

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References to electronic databases: Fabry disease: OMIM 301500.

A. Keilmann (✉)
Department for ENT and Communication Disorders,
University Hospital,
Langenbeckstr. 1,
55101 Mainz, Germany
e-mail: keilmann@kommunikation.klinik.uni-mainz.de

D. Hajioff
Department of Otolaryngology, Southmead Hospital,
Bristol, UK

U. Ramaswami
Department of Paediatric Endocrinology, Diabetes and Metabolism, Addenbrooke's University Teaching Hospital,
Cambridge, UK

Abbreviations

ERT	enzyme replacement therapy
FD	Fabry disease
FOS	Fabry Outcome Survey
FOS-MSSI	Mainz Severity Score Index used in Fabry Outcome Survey
ISO	International Organization for Standardization
PTA	pure-tone average
SD	standard deviation
WHO	World Health Organization

Introduction

Fabry disease (FD; OMIM 301500) is an X-linked, multisystem, lysosomal storage disease with deposition of glycosphingolipids (predominantly globotriaosylceramide, Gb_3) in multiple organs, including the heart, brain, kidney, skin, and gastrointestinal tract. Hearing loss and tinnitus are frequent.

In a previous study on 566 patients in the Fabry Outcome Survey (FOS), 316 reported ear related symptoms (Hegemann et al. 2006). Hearing loss was most often sensorineural and correlated strongly with increasing age at all frequencies. Fabry patients had considerably worse hearing than the general population, and men had earlier and more severe hearing loss than women. These results were confirmed by Ries and colleagues (2007). Normal hearing was common in younger patients (the youngest a 19-year-old), whereas sensorineural hearing loss became more frequent in the older age groups (Germain et al. 2002).

Four girls and two boys aged 7–17 years were examined immediately prior to enzyme replacement therapy (ERT) and again 6 months later (Keilmann 2003). None of these patients had subjective or measurable hearing loss. Tinnitus has been reported in children with FD (Limberger et al. 2007), and in cohort studies of FD in children, hearing loss, tinnitus and vertigo were noted early in childhood and occurred with similar frequency in boys and girls, although the onset of symptoms was 2–5 years later in girls (Ramaswami et al. 2006; Ries et al. 2003). In a large cohort of children with FD, hearing loss was reported in 22%, tinnitus in 31% and vertigo in 25% (Ramaswami et al. 2006).

In this study, we analysed data from patients younger than 18 years with FD, describing hearing impairment and tinnitus using age-appropriate and validated audiometry.

Patients and methods

FOS database

The FOS database is designed to collect data on Fabry patients in a systematic fashion to allow detailed description of functional impairments and to assess the effects of ERT with agalsidase alfa on affected organ systems; database properties have been described elsewhere (Mehta et al. 2004).

Patients from 127 centres in 20 countries contributed to the database. Data were extracted on 18 June 2008. The diagnosis was confirmed in all patients by enzyme assay and/or DNA analysis and in female patients also by mutation analysis. Medical history was assessed with a standardized questionnaire and the signs and symptoms checklist, and concomitant medication was recorded. Patients were asked about subjective hearing impairment, sudden deafness, vertigo and tinnitus. These data were available for 543 patients (258 girls, 285 boys) younger than 18 years at the time point for the evaluation. Depersonalized data were entered into an internet-based database. The Ethics Committee or Institutional Review Board of all participating centres approved FOS, and all parents gave their written informed consent.

Audiometric data on 113 children were collected in the UK ($n=33$: 29%); Germany ($n=30$: 27%); Netherlands ($n=16$: 14%); Italy ($n=13$: 12%); Spain ($n=6$: 5%); Norway ($n=4$: 4%); United States ($n=4$: 4%); Switzerland ($n=3$: 3%); Belgium ($n=2$: 2%); Canada ($n=2$: 2%). Boys were 10.9±4.9 years old at the first audiogram, girls were 11.8±4.3 years old (mean ± standard deviation (SD)).

Pure-tone audiograms were obtained from 101 children. Of 54 children on ERT, 51 received treatment before 18 years of age, 1 was 18 years old, and 2 were 19 years old; 36 children had audiometric examinations before or before and after starting ERT and 18 after starting ERT.

Hearing loss

All patients underwent otoscopy before audiometry. 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 using age-appropriate methods, with bone conduction thresholds and masking as appropriate. All centres followed the International Organization for Standardization (ISO) audiometric guidelines 8253-1 (ISO 1989).

Several sequential audiograms were available for most children. All audiograms for each child were compared to exclude transient conductive hearing losses not related to FD and errors from poor cooperation. If all thresholds in the latest audiogram were no worse than 20 dB, we defined that child's hearing as normal.

To assess the clinical relevance of the audiometric data, we used age-independent clinical guidelines according to the international classification of impairments, disabilities and handicaps (WHO 1980). 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 previously used (Germain et al. 2002; Hegemann et al. 2006).

The authors classified the audiograms independently and discussed the three audiograms where classifications were initially discordant. Audiograms were quantified by age and by hearing status: normal, high-frequency hearing loss, flat hearing loss, and unclear because of poor cooperation.

To assess correlation with other aspects of FD, only children with clear audiogram classifications were

included. Children with unilateral and bilateral high-frequency hearing losses were compared with children with normal hearing (where some audiograms were not completely normal as a result of transient middle-ear disease or poor cooperation). Excluded from the correlation analysis were four children with flat hearing loss, four with unclear audiograms, and one with a pattern typical of noise-induced hearing loss.

Sudden hearing loss

Sudden sensorineural hearing loss has been defined as sensorineural hearing loss of 30 dB or more at three or more adjacent frequencies occurring within 3 days (Hughes et al. 1996). This definition could not be applied to our database, as audiometric data around the time of the suspected sudden hearing loss were unavailable. Hence, we used the subjective statements in the standardized questionnaire.

Tinnitus and vertigo

Tinnitus and subjective vertigo were documented during the clinical consultation; generalized dizziness was not differentiated from true vertigo typical of vestibular dysfunction.

Severity of Fabry disease, tinnitus and hearing loss

Patients with tinnitus and hearing loss were compared with patients without these symptoms with regard to genotype, the general severity of FD, using a slightly modifed version of the Mainz Severity Score Index (FOS-MSSI) (Whybra et al 2004; 2006), and included documenting gastrointestinal symptoms, acroparaesthesia, and retinal vessel tortuosity.

Statistics

The Student's two-sample *t*-test or the Wilcoxon rank-sum test as appropriate were used for statistical analyses, using SAS version 9.1 (SAS Institute Inc., Cary, NC). Values are presented as mean ± SD unless otherwise stated; $p<0.05$ was considered significant.

Results

Hearing loss

Subjective hearing impairment was reported by 179 (33%) of 543 children, 66 (26%) of 258 girls and 113 (40%) of 285 boys.

In all, there were 222 audiograms from 101 children (53 girls, 48 boys) with a median age of 12 years (range 1–18 years). In 78 of 101 children, analysis revealed that hearing thresholds were not worse than 20 dB in any frequency bilaterally (excluding audiograms with likely transient hearing losses and lack of cooperation). It appeared that abnormal audiograms were usually repeated and often returned to normal. Fourteen children had a high-frequency hearing loss (7 unilateral, 7 bilateral) with gradually decreasing threshold, as reported in adult Fabry patients. Four patients had a pan-frequency hearing loss classified as moderate in all audiograms. In these cases, and in those with a transient pan-frequency hearing loss, it remains unclear whether the child had a middle-ear effusion or did not cooperate fully with audiometry. One child presented an isolated loss at 4 kHz bilaterally. In four patients, technical problems impaired the audiometric curve.

Figure 1 demonstrates that high-frequency hearing loss was not present in children younger than 8 years and appeared in the second decade of life in many patients. Most of the unclear and flat audiograms were present in children older than 5 years.

Children on ERT ($n=54$) and those not on ERT ($n=47$) had a similar prevalence of hearing loss: 7 children in each group developed a high-frequency hearing loss. In children on ERT, no child developed a hearing loss during treatment. Therefore, all children were included in the subsequent analyses regardless of ERT. In the 92 children with clear audiogram classification, 44 were untreated; of the 48 children receiving treatment, 45 received treatment before and 3 after 18 years of age.

Sudden deafness

Of the 101 children with audiograms, 2 reported sudden deafness: a 17-year-old boy and a 16-year-old girl. Both had normal hearing at audiometry and were included in the 92 children with clear audiogram classification.

Tinnitus

Tinnitus was reported by 25 (47%) of 53 girls and 19 (40%) of 48 boys with audiograms as compared to 244 (40%) of 612 adult male and 210 (31%) of 672 adult female patients in FOS. Figure 2 shows that the prevalence of tinnitus increases with age. Most patients in their mid-teens reported tinnitus, predominantly girls. Only one girl with tinnitus had a high-frequency hearing loss; 5 children with a unilateral loss and 6 with a bilateral high-frequency hearing loss did not report

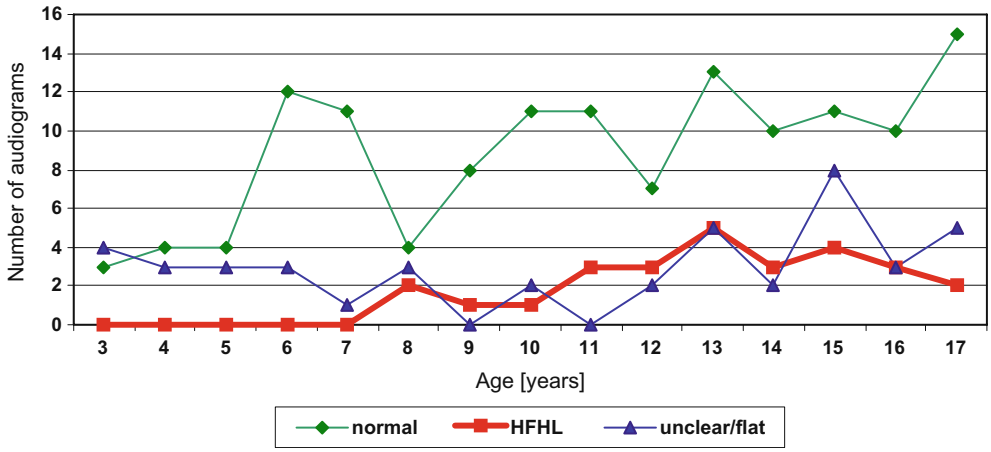

Fig. 1 Number of audiograms with normal hearing, high-frequency hearing loss (HFHL), and unclear result or flat hearing loss

tinnitus at any time. Information about exposure to loud music was unavailable. There was no difference in reported use of concomitant medication between children with or without tinnitus for boys and girls.

Vertigo

Vertigo was reported by 16 girls (30%) and 10 boys (21%) The questionnaire did not differentiate non-specific dizziness from true vertigo, so this symptom was not analysed further.

Ear symptoms and correlation with other symptoms of Fabry disease

Figure 3 shows that girls and boys with tinnitus suffer from more severe FD ($p<0.05$) than those without tinnitus. Disease severity did not differ between children with permanent high-frequency hearing loss (FOS – MSSI = 7.50 ± 4.42 (mean $\pm$ SD)) and those with normal hearing (FOS – MSSI = 9.95 ± 5.63). A second calculation using the FOS MSSI without the weighting for tinnitus still resulted in significant differences in the total FOS-MSSI score between children with and without tinnitus in the sample analysed.

In 14 children with high-frequency hearing loss and 78 children with normal hearing, the frequencies of other features of FD were recorded in the signs and symptoms checklist. These features included gastrointestinal symptoms, acroparaesthesia and tortuous vessels, and appeared in similar proportions in both groups.

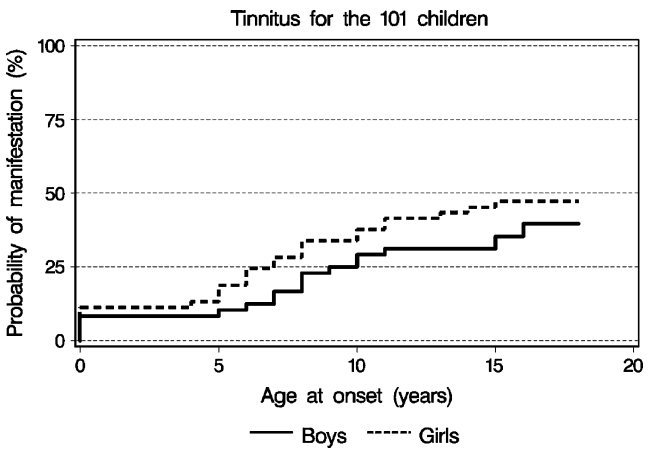

Fig. 2 Frequency of tinnitus reported in the Fabry Outcome Survey (FOS) signs and symptoms checklist. The prevalence of tinnitus increases with age

Discussion

Using the FOS database, we analysed 222 audiograms from 101 children and evaluated standardized medical reports from 543 children with FD. This is the largest survey of hearing function in children with FD. Since audiometric data in the FOS registry were collected from 15 centres in 9 countries for the 101 children with audiograms and from 18 centres in 10 countries for all 113 children with ear examinations, its validity could be criticized, but we have no reason to suspect a significant bias. However, owing to the nature of the data collected in FOS, there may be a degree of selection bias with children needing ERT, representing the severe end of the patient spectrum. Collecting data from large numbers of patients with a rare disease is not possible without using registry data and necessarily accepting its inherent limitations.

Otitis media with effusion is the most common cause of hearing loss in children, affecting up to two-thirds of preschool children (Davidson et al. 1989). The incidence is 10–30% in children younger than 3 years (Seifert et al. 2005) and 3–8% in children younger than

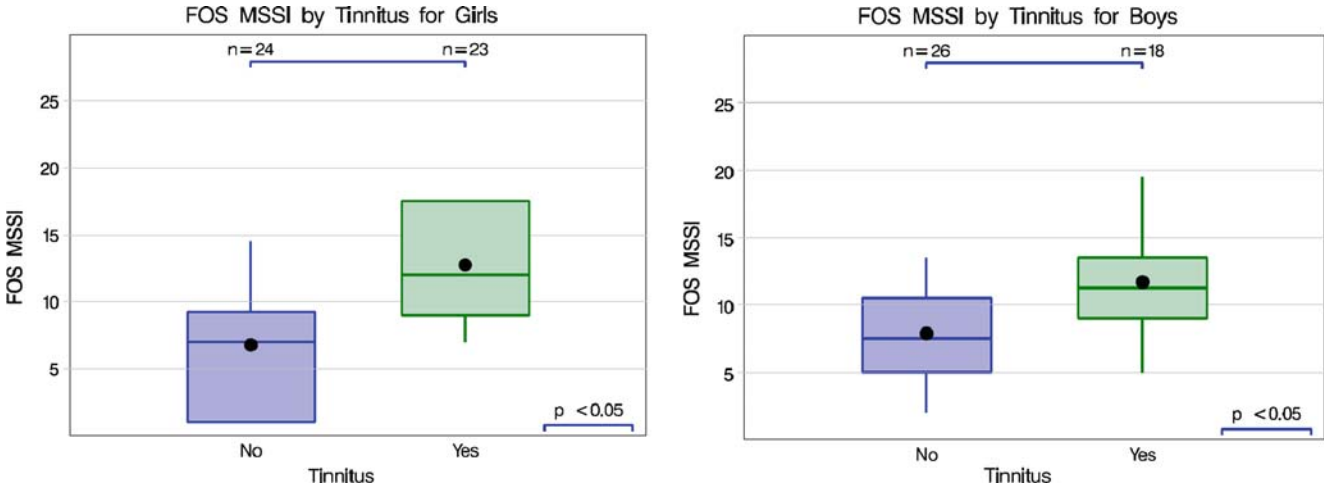

Fig. 3 Both girls and boys with tinnitus have significantly higher disease severity scores (FOS-MSSI: Mainz Severity Score Index used in FOS) than those without tinnitus ($p<0.05$); data from FOS

7 years (Fiellau-Nikolajsen 1980). For children older than 8 years, incidence data are sparse, and most patients in the FOS database are school-aged (median 12 years, range 1–18 years). Unlike in other lysosomal storage diseases, such as mucopolysaccharidoses, young patients with FD do not develop conductive hearing loss more often than children in the normal population. Although subjective hearing loss was reported in one-third of the children, careful evaluation of the audiograms showed that these hearing losses were usually transient.

Transiently elevated thresholds in older children in the Fabry cohort are most likely due to poor cooperation with audiometry. Only 14 older children, 7 of them on ERT, had a high-frequency hearing loss, which is probably the result of FD as the pattern was typical of adult Fabry patients. Our results are consistent with those in the first report about inner-ear function in children with FD (Keilmann 2003), which found that most children with FD hear normally. Sensorineural hearing loss is less common in children with FD than in adults.

As previously demonstrated for cohorts of Fabry patients, the incidence of hearing loss increases with age (Hegemann et al. 2006; Ries et al. 2007). Our results concur with earlier studies and confirm that significant sensorineural hearing loss in FD starts in adolescence. In contrast to the findings in adult patients, we found no clear sex difference.

In adult Fabry patients, sudden hearing loss is more frequent than in the normal population. Hegemann and colleagues (2006) found 32 cases of sudden hearing loss (5.6%) in 566 patients, and men were affected 2.3 times more often than women. The risk of sudden hearing loss in the Fabry population was approximately 10 times greater than in the normal population. In the cohort studied by Ries and colleagues (2007), 10 of 109 patients (12%, men only) had sudden hearing loss. The prevalence of sudden hearing loss in children with FD seems to be much lower, with only two children affected in this study.

Tinnitus is a frequent symptom in adult Fabry patients; it was found in 41.3% of male and 62.5% of female patients (Ries et al. 2007). Estimates of the prevalence of tinnitus clearly depend on how tinnitus is defined, especially in children. Tinnitus is common when children are directly asked about the symptom, but spontaneous complaints are rare. It has been suggested that children over-report tinnitus when questioned to please the questioner (Baguley and McFerran 1999). The prevalence of tinnitus in children with sensorineural hearing loss appears greater than in normal-hearing children and lower in children with profound hearing loss than in children with moderate or severe hearing loss (Baguley and McFerran 1999).

Of 964 Swedish children aged 7 years, 12% reported tinnitus when asked (Holgers 2003). Contrary to prior reports, hearing impairment did not correlate with the prevalence of tinnitus and no sex difference was found. After a lecture in school, noise-induced tinnitus was reported by 53% of 274 children aged 9–16 years; 22.6% reported tinnitus to be annoying sometimes or more often (Holgers and Juul 2006). In data from 1100 children aged 6–16 years, tinnitus was present in 34%, but only 6.5% complained spontaneously (Savastano 2007).

Despite the uncertainty about the prevalence of tinnitus in children, tinnitus seems to be more frequent in Fabry patients. Information about distress due to tinnitus was unavailable in our patients. In adult Fabry

patients, distress from tinnitus is generally low, possibly because of more severe health problems including cardiac and renal disease. In contrast to the normal population, we found a slight sex difference in the frequency of tinnitus in children, with girls more often affected, which differs from earlier findings (Ries et al. 2007). Several drugs are known to cause tinnitus as a side-effect (Lee et al. 2005). Our data showed that the reported use of concomitant medication was low and that there was no relationship to tinnitus.

Hearing loss has been reported to correlate with kidney function and other symptoms typical of FD (Germain et al. 2002; Ries et al. 2007). Patients reporting tinnitus suffered from more severe FD, as measured by the FOS-MSSI. In our study, no significant correlation was found between hearing loss and other features of FD, although the overall severity of FD, as seen in the FOS-MSSI, did correlate with tinnitus.

The effect of ERT on hearing loss in patients in FOS receiving agalsidase alfa was described in a report on 26 patients (8 women, 17 men) with audiometric follow-up at a median of 12 months after starting ERT (Hajioff et al. 2006). It was concluded that hearing is at least stabilized by ERT, and quite possibly improved in ears that are abnormal but not severely affected at baseline.

In summary, hearing loss is a frequent manifestation of FD in childhood and therefore relevant to the development of speech and language and to education. We suggest that careful audiological evaluation with annual age-appropriate audiometry should be part of the assessment and follow-up of all children affected by FD irrespective of age. Future studies should be conducted to evaluate whether hearing loss can be prevented by ERT.

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