J Inherit Metab Dis (2015) 38:351–358
DOI 10.1007/s10545-014-9783-7

ORIGINAL ARTICLE

Hearing loss in adult patients with Fabry disease treated with enzyme replacement therapy

Eefje B. Suntjens · Bouwien E. Smid · Marieke Biegstraaten · Wouter A. Dreschler · Carla E. M. Hollak · Gabor E. Linthorst

Received: 27 July 2014 / Revised: 1 October 2014 / Accepted: 14 October 2014 / Published online: 14 November 2014

Abstract
Introduction Data on prevalence, natural history, and effect of enzyme replacement therapy (ERT) on hearing loss (HL) in Fabry disease (FD) are scarce.
Methods This is a retrospective study with cross-sectional and longitudinal analyses. Low and high-frequency HL in the Dutch FD cohort was studied in four groups: classical and non-classical FD patients with or without ERT. To study effects of ERT, longitudinal data, corrected for age and gender according to ISO-1999 guidelines, were analyzed with mixed models.
Results In the cross-sectional analysis, 107 FD patients (41 males), median age 47.6 years (18.8–80.6) were analyzed. At baseline, i.e., before start of ERT, HL was present in 18 patients (16.8 %), of whom four had bilateral sensorineural HL. HL was more often present in patients with the classical phenotype than non-classical patients ($p<0.01$). Likewise, males had more often HL than females. Compared to the general population, FD patients show a median HL of 8.2 dB at low frequencies ($p<0.01$) and 29.5 dB at ultra-high frequencies ($p<0.01$). Longitudinal analyses ($n=91$) revealed that ERT treated patients show a similar rate of decline, not significantly different from healthy controls.
Conclusion Adult FD patients, especially classical affected males, show impaired hearing. Longitudinal analyses during ERT in these patients demonstrates a decline of HL similar to healthy controls, but HL present before initiation of therapy cannot be reversed. Whether early therapy can prevent hearing loss is unknown.

Introduction

Fabry disease (FD) is an X-linked lysosomal storage disease, affecting glycosphingolipid metabolism due to deficient activity of the lysosomal enzyme alpha-galactosidase A (AGAL) (Brady et al. 1967). AGAL deficiency leads to deposition of predominantly globotriaosylceramide (Gb3) in plasma and lysosomes throughout the body. This ultimately results in organ dysfunction, most likely due to Gb3 accumulation in cells of the microvasculature. In turn, this causes thrombotic and ischemic complications in the brain, heart and kidney (for excellent reviews (Mehta et al. 2009; Brady and Schiffmann 2000; Germain 2002; Rombach et al. 2010b)

Besides renal and cardiac disease and increased risk of strokes, hearing loss is a well known feature of patients with FD. Previous studies showed that HL was predominantly sensorineural. Symptomatic HL was reported in 18–55 % of FD patients, whereas sudden deafness occurred in 6–36 % and tinnitus in 17–53 %, respectively. FD patients perform considerably worse on audiological tests than healthy controls, with an earlier onset of HL for men than for women (MacDermot et al. 2001; Germain et al. 2002; Conti and Sergi 2003; Hegemann, Hajioff et al. 2006; Ries et al. 2007; Sakurai et al. 2009; Sergi et al. 2010; Kaminsky et al. 2013)

Communicated by: Verena Peters

Electronic supplementary material The online version of this article (doi:10.1007/s10545-014-9783-7) contains supplementary material, which is available to authorized users.

E. B. Suntjens · B. E. Smid · M. Biegstraaten · C. E. M. Hollak · G. E. Linthorst (✉)
Sphinx-Amsterdam Lysosome Center, Department of Endocrinology and metabolism, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
e-mail: g.e.linthorst@amc.nl

W. A. Dreschler
Department of Clinical & Experimental Audiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

(see also Supplementary Table 1). Though these symptoms do not influence life expectancy, they can have a negative impact on quality of life (Narozny et al. 2014).

The introduction of enzyme replacement therapy (ERT) with agalsidase beta (Fabrazyme, Genzyme-Sanofi) and agalsidase alfa (Replagal, Shire) in 2001 has had a profound impact on management of FD patients. ERT has been associated with stabilization of kidney function and improvement of cardiac structure and function in some patients, but progression of disease is seen in others (Watt et al. 2010; Rombach et al. 2013; Weidemann et al. 2013). The few studies that examined the effect of ERT on HL showed conflicting results: some reported improvement (Hajioff et al. 2003a, b, 2006), whereas others suggested stability (Palla et al. 2007; Sergi et al. 2010) (see also supplementary Table 1). These studies examined only small groups (n = 15 to 26) of FD patients, and made no distinction between FD phenotype. This is of importance as it is expected for HL to be more prominent in the more severely affected, classical male FD patients, than in females and the so-called late onset variants, or non-classical patients (Altarescu et al. 2001; Ries et al. 2007).

Our aim was to investigate HL in the conventional range of audiometric frequencies in the entire Dutch cohort of classic and non-classical FD patients. Second, we examined HL in ultra high frequencies (above 8 kHz). Third, the long-term effects of ERT on hearing were studied.

Methods

Patients

The Academic Medical Center (AMC) is the national referral center for FD in the Netherlands. Audiological test results (baseline and most cases follow-up) were available for 130 adult FD patients. The study cohort was divided into four groups: classical and non-classical FD patients (following the criteria by (van der Tol et al. 2013)) with or without ERT. In short, a classical (definite) FD diagnosis was defined as: AGAL enzyme activity in leukocytes (<5 % of the mean reference value, males only) *and* a GLA mutation and *either one or both* of the following criteria: i) an increase in plasma (lyso) Gb3 (in the range of classically affected males), ii) ≥1 characteristic features of FD (cornea verticillata, angiokeratoma, neuropathic pain), iii) a family member with a definite diagnosis of classical FD. A diagnosis of FD is uncertain when a patient presents with a clinical picture of a single non-specific symptom such as left ventricular hypertrophy or proteinuria *and* a GLA mutation, that does not fit the criteria above. If in this patient a characteristic storage pattern of an affected organ on electron microscopy (EM) analysis is shown, a FD diagnosis is definite and classified as non-classical, biopsy proven FD. We excluded patients with an 'uncertain FD diagnosis' in whom no biopsy was available to confirm a diagnosis of FD ((van der Tol et al. 2013), n=7) and patients in whom a GLA mutation appeared non-pathogenic as proven by a negative organ biopsy (n=16).

To quantify the severity of FD, the MSSI score was calculated at baseline in ERT treated patients and at the most recent evaluation in untreated patients: <20 mild disease, 20–40 moderate disease, and >40 severe disease (Whybra et al. 2004).

Time of follow-up was defined as the number of years between first (baseline) and last available audiogram. First available audiogram was in all cases before ERT. ERT was given with either agalsidase alfa 0.2 mg/kg/eow or agalsidase beta 0.2 or 1.0 mg/kg/eow. As superiority of one of these drugs has not been proven so far, these were combined in our analyses (Vedder et al. 2007; Sirrs et al. 2014).

This is a retrospective and non-interventional study, which according to Dutch law does not require approval by the hospital's Ethical Committee. Patients consented to use their anonymized data as collected in the AMC database for research purposes.

Auditory testing

Audiograms were made yearly in treated, and every two years in untreated FD patients. Audiological evaluation consisted of pure tone audiometry (PTA): air conduction thresholds for the conventional range of frequencies (0.25, 0.5, 1, 2, 4, and 8 kHz), high frequencies (8, 10, and 12 kHz), and bone conduction (0.5, 1, and 2 kHz). Frequencies above 8 kHz were initially not routinely measured and are therefore missing in some patients. The following parameters were used to classify HL;

- Average HL (PTA) for air conduction thresholds at low frequencies (0.5, 1, and 2 kHz): $PTA_{.5,1,2}$
- Average HL for air conduction thresholds at high frequencies (4 and 8 kHz): $PTA_{4,8}$
- Average HL for air conduction thresholds at ultra high frequencies (8–12 kHz): $PTA_{8,10,12}$.

Classification of HL

The degree of HL was categorized both *with* and *without* correction for age and gender. To classify **uncorrected** HL, an age-independent clinical guideline was used (International classification of impairments, disabilities, and handicaps, WHO, May 1980, Geneva, Switzerland) which implies that for each subject, impairment was classified on the basis of low frequency HL ($PTA_{.5,1,2}$) of the most affected ear (irrespective of type HL). It concerns the

following pure-tone threshold ranges: normal (0–25 dB HL), mild (26–40 dB HL), moderate (41–55 dB HL), moderately severe (56–70 dB HL), severe (71–90 dB HL), and profound (>91 dB HL). Following this guideline, we defined HL as $PTA_{.5,1,2}$>25 dB. Patients with HL >40 dB were believed to have clinically relevant HL, as this is the degree of HL at which hearing aids are generally recommended. (according to WHO classification criteria) Asymmetric HL was defined as a difference of more than 10 dB for low frequency HL between the right and left ear. An internationally accepted age-independent classification for high tone loss is not available.

To study the magnitude of HL due to FD, an age and gender dependent threshold correction was used, based on median values (P50) of HL for otologically normal and healthy subjects of the same age and gender, according to ISO-1999 (Standardization 1990). For each subject, impairment was classified using the parameters of the most affected ear. In the absence of ISO-1999 standards for the high frequency data (8-12Khz), we used the internal standard of our hospital to correct values for age and gender. Internal age-corrected reference values based on data of Dreschler et al. (Dreschler et al. 1985) were used, that fitted with the method of Johansson and Arlinger (Johansson and Arlinger 2002).

Type of hearing loss

The type of HL was classified as sensorineural, conductive, or mixed in patients with HL ($PTA_{.5,1,2}$>25 dB) as follows. Sensorineural HL was diagnosed when the HL did not show an averaged air-bone gap of ≥10 dB. Conductive HL was defined as a HL with an average air-bone gap of >10 dB for 0.5, 1, and 2 kHz and normal bone conduction thresholds (≤25 dB HL). Mixed HL was defined as a bone conduction threshold greater than 25 dB HL in combination with an average air-bone gap of >10 dB.

Longitudinal analyses in patients with classical FD were performed using audiometric data, corrected for age and gender. For these analyses impairment was classified according to symmetry and type of HL. In patients with a symmetric hearing loss the mean hearing loss of both ears was used. In patients who suffered from asymmetric HL, we included the ear with a purely sensorineural HL (conductive HL was often present in one of the ears). In three cases we found asymmetry due to an asymmetrical sensorineural HL, here we only included the better ear.

Statistical analyses

Statistical analyses were performed using SPSS 20.0 (IBM, Chicago). Baseline results are expressed using percentages or medians. Mann Whitney U and Chi square tests were used to test for differences between groups. To determine whether HL in patients differs from healthy subjects, the Wilcoxon signed-rank test was used with age and gender corrected data as continuous variable and zero as hypothesized median. Associations between variables are described with the use of Spearman's rho. Long term follow-up was studied with a mixed model with repeated covariance type AR(1) with corrected data. Mean HL of the right and left ear (low, high, and ultra high frequencies: $PTA_{.5,1,2,}$ $PTA_{4,8}$, and $PTA_{8,10,12}$) was set as dependent variable with time point as fixed covariate. A p-value <0.05 was considered statistically significant.

Results

General characteristics of patients

Baseline audiograms (i.e., pre-treatment) were available for 107 FD patients (41 males). Median age at the time of baseline audiogram was 47.6 years (range 18.8–80.6 years) (Table 1). In general, ERT treated patients were older (median age 51.2 years vs 41.7 years, p <0.05) and more severely affected (median MSSI 19.5 vs 9.0, p <0.01) than untreated patients, see Table 1 for clinical information and supplementary Table 2 (available online) for an overview of GLA mutations in the cohort.

Baseline hearing loss

Type of hearing loss

At baseline, HL ($PTA_{.5,1,2}$>25 dB) was present in 18 out of the 107 patients studied (16.8 %, 12 males) and was predominantly sensorineural (50 %). HL was bilateral in nine patients (sensorineural, mixed, and conductive in respectively four, four, and one patients) and unilateral HL in the remaining nine patients (sensorineural, mixed, and conductive in respectively five, two, and two patients). In total 12 out of 107 patients demonstrated asymmetric HL (median absolute inter-aural difference was 25 dB, range 13.3–68.3 dB).

Degree of hearing loss: uncorrected data

Table 1 illustrates the degree of HL at baseline, categorized by gender and phenotype, using uncorrected data. Of the 18 patients with HL, nine had mild HL (26–40 dB HL). Clinically relevant HL (>40 dB HL) was present in the remaining nine patients (8.4 %). These were predominantly classically

Table 1 Baseline characteristics of patients with Fabry disease (FD). Hearing loss (HL) is classified according to WHO International classification of impairments, disabilities, and handicaps

Characteristics	Classical FD males	Classical FD females	Non-classical FD males	Non-classical FD females
n=	32	59	9	7
Age (years)				
Median;	44.3	47.7	63.6	39.3
Range;	19.8–70.6	18.8–80.6	53.8–73.4	31.2–65.3
ERT (n, %)	29 (91 %)	36 (61 %)	6 (67 %)	2 (29 %)
MSSI score				
Median (range);	21 (8–46)	14 (1–35)	19 (10–29)	2 (0–14)
Follow up (years)				
Median (range);				
ERT treated	6 (0–12)	7 (0–11)	3 (2–11)	0
No ERT	1 (1–2)	6 (0–10)	6 (6–8)	4 (0–8)
Baseline HL (n, %)				
Normal	22 (68.8 %)	54 (91.5 %)	7 (77.8 %)	6 (85.7 %)
Mild	4 (12.5 %)	4 (6.8 %)	1 (11.1 %)	–
Moderate	2 (6.3 %)	1 (1.7 %)	–	–
Moderate-severe	1 (3.1 %)	–	–	–
Severe	3 (9.4 %)	–	1 (11.1 %)	–
Profound	–	–	–	1 (14.3 %)
GFR (mL/min/1.73 m^2)				
Median;	109.3	104.8	81.9	105.3
Range;	23–151	45–151	18–106	86–120
LVH (n, %)	8 (25 %)	13 (22 %)	4 (44 %)	1 (14.3 %)
Any clinical event (n, %)	8 (25 %)	6 (10 %)	8 (89 %)	0 (0 %)
- Cardiac	3 (9 %)	1 (2 %)	5 (56 %)	0 (0 %)
- CVA/TIA	2 (6 %)	4 (7 %)	2 (22 %)	0 (0 %)
- Dialysis/renal transplant	3 (9 %)	1 (2 %)	1 (11 %)	0 (0 %)

Abbreviations GFR glomerular filtration rate estimated by CKD-EPI formula. *LVH* left ventricular hypertrophy. Any clinical event is defined as: stroke, *TIA* cardiac event, dialysis or a kidney transplant. A cardiac event is defined as: symptomatic cardiac arrhythmias, implant cardioverter defibrillator, myocard infarct, percutan transluminal coronary angioplasty, coronary artery bypass grafting or admission to a hospital due to heart failure

affected males (n=5). In the classical FD group, 15/91 patients (16.5 %) showed HL ranging from 26.7 to 90.0 dB. Male patients were more likely to suffer from HL than female patients (p<0.01). However, classical patients did not suffer more often from HL than non-classical patients (p=0.823). When we divided our cohort into four groups based on gender and phenotype, male classical FD patients did not suffer more often from HL than male non-classical FD patients (p=0.599). Likewise, female classical FD patients did not suffer more often from HL than female non-classical FD patients (p=0.613).

Degree of hearing loss: age and gender corrected data

Baseline audiograms for the ultra high frequencies (>8 kHz) were not available in 23 patients. Analyses of the $PTA_{8,10,12}$ data were therefore based on a subset of the patients (Table 2).

Analyses of age and gender corrected audiological data in the whole FD cohort revealed a median HL of 8.2 dB (range −5.5;91.5 dB) for $PTA_{.5,1,2}$, 10.0 dB (range −9.5;104.1 dB) for $PTA_{4,8}$, and 29.5 dB (range; −17.1–106.5 dB) for $PTA_{8,10,12}$. Corrected HL was more severe in high frequencies than low frequencies. In comparison to healthy age and gender matched controls this was statistically significant in almost all groups (p <0.01) except for the ultra high frequency data in females with the non-classical phenotype (Table 2).

At baseline, male patients had more severe HL than in female patients in low, high, and ultra high-frequencies (all p<0.001). Differences in corrected HL between classical and non-classical patients (males and females combined) were only seen for ultra high frequencies (p <0.01), but not for low and high frequencies (p = 0.29 and p =0.19). Patients on ERT showed more severe HL than non-ERT treated patients, both in low and high frequencies (p<0.05 and p<0.01, respectively). In the ultra high frequencies, this difference was not significant (p=0.09). Correlation coefficients between disease severity and degree of HL for low (Spearmans rho=0.51) and high (Spearmans rho =0.35) frequencies were weak but significant (both p<0.01).

Table 2 Age-gender corrected hearing loss at baseline

		n=	Median (dB HL)	Range (dB HL)	*P*-value
Low frequency ($PTA_{.5,1,2}$)					
Classical FD	♂	32	13.3	−5.5;87.2	0.000*
	♀	59	5.7	−2.1;47.4	0.008*
Non-classical FD	♂	9	11.1	2.6;65.7	0.000*
	♀	7	6.7	0.8;91.5	0.018*
High frequency ($PTA_{4,8}$)					
Classical FD	♂	32	33.2	0.0;104.1	0.000*
	♀	59	8.1	−6.1;96.2	0.038*
Non-classical FD	♂	9	6.9	−9.5;45.7	0.000*
	♀	7	9.6	2.2;95.2	0.018*
Ultra high frequency ($PTA_{8,10,12}$)					
Classical FD	♂	24	58.3	21.7–106.5	0.000*
	♀	49	25.5	−17.1–92.6	0.028*
Non-classical FD	♂	6	9.0	3.4–33.9	0.000*
	♀	5	22.5	−1.5–97.2	0.080

*statistical significant difference between FD groups and age-and gender corrected healthy controls

Natural history and effect of ERT on hearing loss

Follow-up data were available for 91 classical FD patients, of whom 65 received ERT (71.4 %). Based upon the protocol specified frequency of audiological evaluations in the studied cohort, 466 audiograms should have been performed. There were 454 audiograms available, indicating <3 % was missing. Longitudinal analyses revealed that at baseline (pre-treatment) classical ERT treated males, have more severe HL in all frequencies ($p<0.05$) (Table 3). The same holds true for ERT treated and untreated female patients with a classical phenotype ($p<0.05$). However, the slope of HL was not significantly different from healthy controls (i.e., zero) in classical males and females treated with ERT. Thus, after baseline, progression of HL in ERT treated patients is similar to healthy controls (Table 3 and Fig. 1). Figure 1d suggests a favorable effect of ERT on high tones in females, however, this was not statistically significant ($p=0.08$). Since only three untreated classically affected males were included, no conclusions could be drawn about their natural history.

Discussion

With this study we confirm the high prevalence of HL in FD patients, especially present in ultra high-frequencies (>8 kHz). HL was most prominent in male patients with the classical phenotype. Significant HL was already present at initial assessments (baseline), while additional follow-up measurements revealed that HL in ERT treated patients with classical FD follows the same course as healthy controls. Thus, HL present before initiation of ERT, is not reversed by long term treatment with ERT.

A thorough comparison of the prevalence of HL with other reports is hampered by the use of different cut off values and methods (see Supplementary Table 1). Furthermore, study cohorts differed in disease severity and gender distribution.

Table 3 Longitudinal analysis of age and gender corrected HL divided by low, high, and ultra high frequencies

	n	Intercept (95 % CI)	T (95 % CI)
Low frequency ($PTA_{.5,1,2}$)			
Classical FD males	32	12.9 (8.5;17.4)*	0.3 (−0.2;0.8)
ERT treated	29	13.1 (8.3;17.9)*	0.3 (−0.2;0.8)
Untreated	3	11.7 (−9.5;32.9)	0.5 (−23.7;24.7)
Classical FD females	59	5.6 (3.5;7.4)*	0.1 (−0.2;0.4)
ERT treated	36	5.9 (3.2;8.6)*	0.1 (−0.3;0.5)
Untreated	23	4.8 (1.8;7.8)*	0.2 (−0.1;0.5)
High frequency ($PTA_{4,8}$)			
Classical FD males	32	29.2 (21.9;36.5)*	0.6 (−0.2;1.4)
ERT treated	29	28.4 (21.1;35.6)*	0.7 (−0.1;1.5)
Untreated	3	37.5 (−49.2;124.2)	−1.8 (−14.0;10.3)
Classical FD females	59	8.7 (5.1;12.4)*	0.4 (−0.1;0.8)
ERT treated	36	10.4 (4.9;16.0)*	0.3 (−0.3;1.0)
Untreated	23	6.0 (2.4;9.6)*	0.4 (−0.2;1.0)
Ultra high frequency ($PTA_{8,10,12}$)			
Classical FD males	31	53.9 (46.9;61.0)*	0.1 (−1.0;1.2)
ERT treated	28	54.5 (46.8;62.1)*	0.0 (−1.1;1.2)
Untreated	3	49.3 (11.0;87.5)*	0.6 (−3.8;5.0)
Classical FD females	59	24.0 (19.7;28.3)*	-0.1 (−0.6;0.5)
ERT treated	36	24.1 (18.0;30.3)*	−0.2 (−1.0;0.5)
Untreated	23	23.7 (18.0;29.5)*	0.3 (−0.4;1.0)

The intercept represents mean additional hearing loss present at baseline (dB), whereas T represents the slope of hearing loss * represents a statistically significant difference *($p< 0.05$)* compared to healthy controls

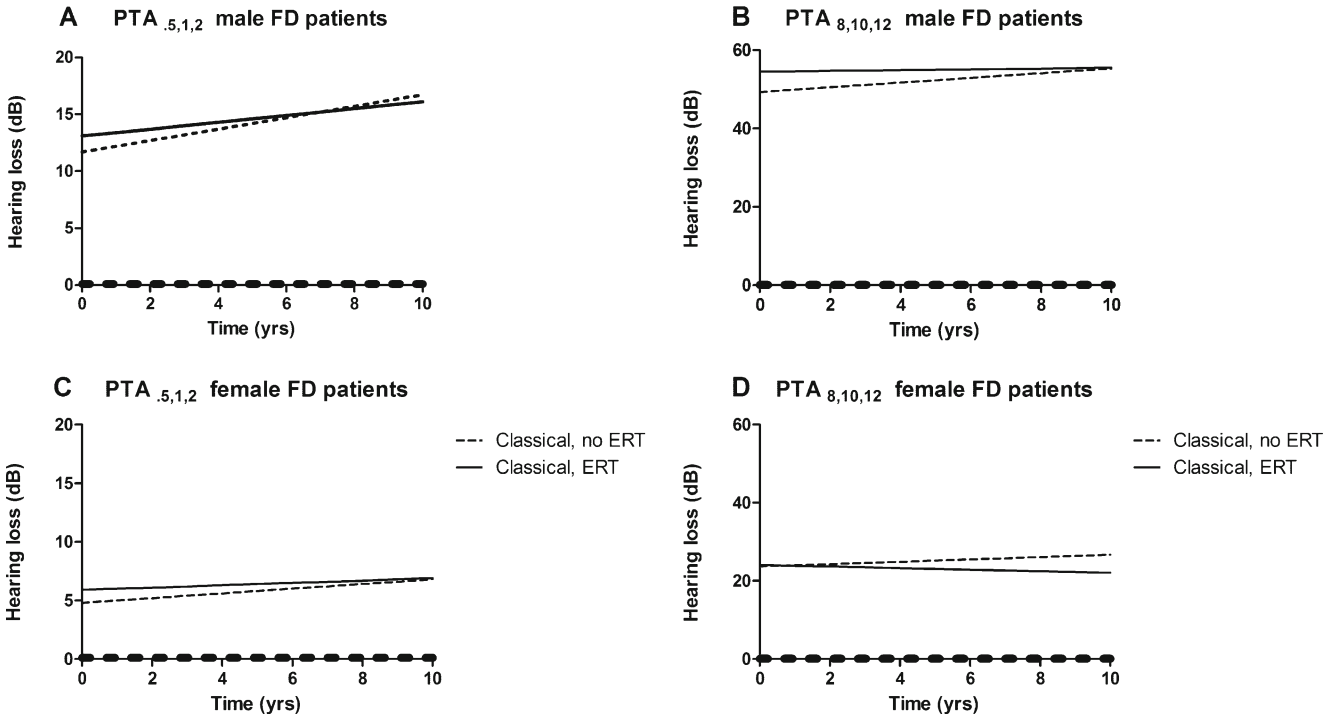

Fig. 1 Changes in hearing loss over time in patients with classical FD. (a) $PTA_{.5,1,2}$ HL in male patients. (b) $PTA_{8,10,12}$ HL in male patients. (c) $PTA_{.5,1,2}$ HL in female patients. (d) $PTA_{8,10,12}$ HL in female patients. Since corrected data were used, healthy controls should follow the y=o line, marked with black circles

Two studies used identical cut-off values for uncorrected HL (WHO-criteria mean PTA of >25 dB). A comparable prevalence was described in a cohort of rather similar age and gender (16.8 % vs. 16 %) (Hegemann et al. 2006). In contrast, HL in our study was much lower in classically affected males, which is probably explained because they were more severely affected as evidenced by a high percentage of end stage renal failure (±70 %) (Germain et al. 2002).

Our study, with the longest ERT follow-up so far, demonstrated that the slope of decline of HL in treated patients with classical FD is similar to healthy controls. As the natural course of HL in classically affected patients is not well known, we cannot exclude the possibility that HL in ERT treated patients could have deteriorated more rapidly if they had been left untreated. Adequate comparison with untreated patients in our cohort was hampered by the fact that only three classically affected males and 23 classically affected females had untreated longitudinal follow-up. In addition, bias by indication limits a robust analysis, as in general those left untreated had milder disease. Previous studies (see appendix Table 2), which are mostly open-label studies, indicated mixed results on the effects of ERT: either ERT had a very mild positive effect on HL (Hajioff et al. 2003a, b, 2006), or symptoms remained stable over time. Most results, however, suggested that ERT does not improve already present HL, but at best may provide some protection for the inner ear epithelium, which will be seen as stabilization of hearing loss (Palla et al. 2007; Sergi et al. 2010).

The pathogenesis of HL in FD is largely unknown. A histological study in FD demonstrated stria vascularis and spiral ligament atrophy, outer hair cell loss and decreased numbers of spiral ganglion cells on autopsy. Similar findings were reported by Sakurai et al. in an AGAL deficient mouse model (Schachern et al. 1989; Sakurai et al. 2010). In analogy to Krabbe's diseases where neurotoxic sphingosines accumulate, it has been postulated that globotriaosylsphingosine (lyso-Gb3), invariably elevated in all classical FD patients, is neurotoxic (Aerts et al. 2008). Although limited evidence is available to support this hypothesis, Rombach et al. showed a statistical trend that plasma lyso-Gb3 is correlated to hearing loss. Whether this is causally related should be the focus of future experimental research (Rombach et al. 2010a, b). In addition, Biegstraaten et al. found a relation between life-time lyso-Gb3 exposure and small fiber neuropathy (Biegstraaten et al. 2012). Whether the small fiber neuropathy causing the characteristic acroparesthesias in FD have similarities with the pathology of the inner ear is unclear. Yet, it is of interest to note that acroparesthesias in classically affected patients usually manifest between ages 5 and 20. In this study we noted HL before the initial assessment, suggesting that hearing loss occurs earlier, possibly during childhood or early adulthood. Ries et al. observed that detectable hearing loss starts in the second and fourth decades of life for males and female patients, respectively (Ries et al. 2007). Audiological testing in children is needed to demonstrate whether hearing loss indeed occurs at early age.

This study has some limitations. In order to study the effect of phenotype on HL, patients were categorized in different groups, which resulted in limited patients numbers, especially in the non-classical patient cohorts. Thus, our data in non-classical patients should be interpreted with caution. In addition, due to the retrospective nature of this study, risk factors which may influence HL were not collected (ototoxic medication, noise exposure, otologocial surgery, trauma, genetic hearing loss). In addition, comparison with untreated patients with identical disease severity was not possible. However, despite these shortcomings, this remains the largest and most robust audiological study in FD patients on ERT so far.

In conclusion, we demonstrated that FD patients have impaired hearing, which was already present at baseline (i.e., before start of ERT), with classical and male patients being more severely affected. During follow-up, further deterioration of hearing in treated patients with classical FD is comparable to the rate of decline in healthy controls. We therefore hypothesize that the involvement of the auditory system already occurs early in life (before adulthood). This necessitates the evaluation of HL in children with FD. This study also indicates that there is probably no need to perform a yearly audiological evaluation, as HL progresses slowly. Following an extensive audiological evaluation at baseline, follow-up assessments can be guided by clinical symptoms.

Compliance with ethics guidelines

Conflicts of interest Eva Suntjens and Wouter Dreschler declare no conflict of interests

Bouwien Smid has received travel support and reimbursement of expenses from Actelion, Shire HGT or Genzyme.

Marieke Biegstraaten, Carla Hollak and Gabor Linthorst have received travel support, honoraria for consultancies and speakers fees from Actelion, Genzyme, Shirt HGT, Protalix or Amicus. All fees are donated to the Gaucher Stichting or the AMC Medical Research for research support.

Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2005. Informed consent was obtained from all patients for being included in the study.

References

Aerts JM, Groener JE, Kuiper S et al (2008) Elevated globotriaosylsphingosine is a hallmark of Fabry disease. Proc Natl Acad Sci U S A 105(8):2812–2817

Altarescu GM, Goldfarb LG, Park KY et al (2001) Identification of fifteen novel mutations and genotype-phenotype relationship in Fabry disease. Clin Genet 60(1):46–51

Biegstraaten M, Hollak CE, Bakkers M, Faber CG, Aerts JM, van Schaik IN (2012) Small fiber neuropathy in Fabry disease. Mol Genet Metab 106(2):135–141

Brady RO, Schiffmann R (2000) Clinical features of and recent advances in therapy for Fabry disease. JAMA J Am Med Assoc 284(21): 2771–2775

Brady RO, Gal AE, Bradley RM, Martensson E, Warshaw AL, Laster L (1967) Enzymatic defect in Fabry's disease. Ceramidetrihexosidase deficiency. N Engl J Med 276(21):1163–1167

Conti G, Sergi B (2003) Auditory and vestibular findings in Fabry disease: a study of hemizygous males and heterozygous females. Acta Paediatr (Oslo, Norway: 1992) 92(Supplement443):33–37, discussion 27

Dreschler WA, vd Hulst RJ, Tange RA, Urbanus NA (1985) The role of high-frequency audiometry in early detection of ototoxicity. Audiol Off Organ Int Soc Audiol 24(6):387–395

Germain DP (2002) Fabry's disease (alpha-galactosidase-A deficiency): physiopathology, clinical signs, and genetic aspects. J Soc Biol 196(2):161–173

Germain DP, Avan P, Chassaing A, Bonfils P (2002) Patients affected with Fabry disease have an increased incidence of progressive hearing loss and sudden deafness: an investigation of 22 hemizygous male patients. BMC Med Genet 3:10

Hajioff D, Enever Y, Quiney R, Zuckerman J, Mackermot K, Mehta A (2003a) Hearing loss in Fabry disease: the effect of agalsidase alfa replacement therapy. J Inherit Metab Dis 26(8):787–794

Hajioff D, Goodwin S, Quiney R, Zuckerman J, MacDermot KD, Mehta A (2003b) Hearing improvement in patients with Fabry disease treated with agalsidase alfa. Acta Paediatr (Oslo, Norway : 1992) 92(Supplement 443):28–30, discussion 27

Hajioff D, Hegemann S, Conti G et al (2006) Agalsidase alpha and hearing in Fabry disease: data from the Fabry Outcome Survey. Eur J Clin Investig 36(9):663–667

Hegemann S, Hajioff D, Conti G et al (2006) Hearing loss in Fabry disease: data from the Fabry Outcome Survey. Eur J Clin Investig 36(9):654–662

Johansson MS, Arlinger SD (2002) Hearing threshold levels for an otologically unscreened, non-occupationally noise-exposed population in Sweden. Int J Audiol 41(3):180–194

Kaminsky P, Noel E, Jaussaud R et al (2013) Multidimensional analysis of clinical symptoms in patients with Fabry's disease. Int J Clin Pract 67(2):120–127

MacDermot KD, Holmes A, Miners AH (2001) Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males. J Med Genet 38(11):750–760

Mehta A, Beck M, Elliott P et al (2009) Enzyme replacement therapy with agalsidase alfa in patients with Fabry's disease: an analysis of registry data. Lancet 374(9706):1986–1996

Narozny W, Gromnicki M, Majkowicz M, Kuczkowski J, Sochaczewska A (2014) Quality of life patients with sudden sensorineural hearing loss. Otolaryngol Polska Polish Otolaryngol 68(2):69–76

Palla A, Hegemann S, Widmer U, Straumann D (2007) Vestibular and auditory deficits in Fabry disease and their response to enzyme replacement therapy. J Neurol 254(10):1433–1442

Ries M, Kim HJ, Zalewski CK et al (2007) Neuropathic and cerebrovascular correlates of hearing loss in Fabry disease. Brain J Neurol 130(Pt 1):143–150

Rombach SM, Dekker N, Bouwman MG et al (2010a) Plasma globotriaosylsphingosine: diagnostic value and relation to clinical manifestations of Fabry disease. Biochim Biophys Acta 1802(9): 741–748

Rombach SM, Twickler TB, Aerts JM, Linthorst GE, Wijburg FA, Hollak CE (2010b) Vasculopathy in patients with Fabry disease: current controversies and research directions. Mol Genet Metab 99(2):99–108

Rombach SM, Smid BE, Bouwman MG, Linthorst GE, Dijkgraaf MG, Hollak CE (2013) Long term enzyme replacement therapy for Fabry disease: effectiveness on kidney, heart and brain. Orphanet J Rare Dis 8:47

Sakurai Y, Kojima H, Shiwa M, Ohashi T, Eto Y, Moriyama H (2009) The hearing status in 12 female and 15 male Japanese Fabry patients. Auris Nasus Larynx 36(6):627–632

Sakurai Y, Suzuki R, Yoshida R et al (2010) Inner ear pathology of alpha-galactosidase A deficient mice, a model of Fabry disease. Auris Nasus Larynx 37(3):274–280

Schachern PA, Shea DA, Paparella MM, Yoon TH (1989) Otologic histopathology of Fabry's disease. Ann Otol Rhinol Laryngol 98(5 Pt 1):359–363

Sergi B, Conti G, Paludetti G, Interdisciplinary Study Group On Fabry D (2010) Inner ear involvement in Anderson-Fabry disease: long-term follow-up during enzyme replacement therapy. Acta Otorhinolaryngol Ital organo ufficiale della Societa italiana di otorinolaringologia e chirurgia cervico-facciale 30(2):87–93

Sirrs SM, Bichet DG, Casey R et al (2014) Outcomes of patients treated through the Canadian Fabry disease initiative. Mol Genet Metab 111(4):499–506

Standardization IOo (1990) Acoustics — determination of occupational noise exposure and estimation of noise-induced hearing impairment 1990REP. No. ISO 1999

van der Tol L, Smid BE, Poorthuis BJ, et al (2014) A systematic review on screening for Fabry disease: prevalence of individuals with genetic variants of unknown significance. J Med Genet 5(11):1–9

Vedder AC, Linthorst GE, Houge G et al (2007) Treatment of Fabry disease: outcome of a comparative trial with agalsidase alfa or beta at a dose of 0.2 mg/kg. PLoS One 2(7):e598

Watt T, Burlina AP, Cazzorla C et al (2010) Agalsidase beta treatment is associated with improved quality of life in patients with Fabry disease: findings from the Fabry Registry. Genet Med Off J Am Coll Med Genet 12(11):703–712

Weidemann F, Niemann M, Stork S et al (2013) Long-term outcome of enzyme-replacement therapy in advanced Fabry disease: evidence for disease progression towards serious complications. J Intern Med 274(4):331–341

Whybra C, Kampmann C, Krummenauer F et al (2004) The Mainz Severity Score Index: a new instrument for quantifying the Anderson-Fabry disease phenotype, and the response of patients to enzyme replacement therapy. Clin Genet 65(4):299–307