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Inner ear involvement in Fabry disease: Clinical and audiometric evaluation of a large cohort of patients followed in a reference centre

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ABSTRACT

Background: Fabry disease (FD) is a lysosomal storage disorder (LSD) that involves the cochleovestibular system. Tinnitus and progressive sensorineural hearing loss are frequent complains. A stabilization of hearing function has been reported with enzyme replacement therapy (ERT). This study aims to characterize the inner ear involvement, identify factors associated to hearing loss and evaluate the effect of ERT on the hearing function of FD patients.

Methods: We reviewed the clinical records of patients with confirmed diagnosis of FD followed in a Reference Centre on LSD in the North of Portugal.

Results: We included a total of 122 patients with a mean age of 47.1 ± 17.6 years and 48.3% males. Hearing loss was reported by 26.2% of the patients and 23.0% mentioned tinnitus. Pure tone audiometry revealed sensorineural hearing loss in 36.9% of the cases. FD patients presented worse age-adjusted hearing thresholds in all analysed frequencies compared to the normal population ($p = .001$). Patients with hearing loss presented a significantly higher value of microalbuminuria ($p = .001$) and a higher frequency of acroparesthesias ($p = .032$). Patients presented a comparable hearing level one year after starting ERT ($p = .384$).

Conclusions: In FD, hearing loss is common and age-matched hearing thresholds by frequency are worse than in the general population. Hearing loss was associated to the presence of acroparesthesias and higher values of microalbuminuria. Hearing loss stabilized in patients under ERT. A careful cochleo-vestibular evaluation should be part of the clinical assessment of FD.

1. Introduction

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by mutations of the GLA gene and subsequent deficient activity of the enzyme alpha-galactosidase A (α-Gal A). The enzymatic defect results in lysosomal accumulation of glycosphingolipids, predominantly globotriaosylceramide (GB3), leading to multiorgan damage and a wide spectrum of clinical manifestations (Brady et al., 1967; Desnick et al., 2001; Germain et al., 2002).

The prevalence of FD has been reported to range from 1 in 117000 live births to 1 in 40000 males (Desnick et al., 2001). Later, Spada et al. reported a higher FD prevalence of 1 in 3100 male newborns due to the high frequency of later onset phenotypes (Spada et al., 2006).

Male patients have little to no residual α-Gal A activity, facing the full spectrum of disease symptoms. In females, FD presentation is variable, depending on the normal to mutant ratio of α-Gal A in the different tissues due to the random X-chromosome inactivation (Germain, 2010; Echevarria et al., 2016). Clinical manifestations may arise early, in childhood or adolescence, and include acroparesthesias, cornea verticillata, angiokeratomas and microalbuminuria or proteinuria. In adulthood, patients may develop left ventricular hypertrophy, heart failure, dysrhythmias, cardiac conduction disturbances, renal failure, cerebrovascular events and otologic manifestations (Tuttolomondo et al., 2013a, 2013b).

Indeed, the multi-systemic nature of FD does not spare the cochleovestibular system. Nevertheless, the studies specifically focusing on the inner ear involvement by FD are few and based on small cohorts of patients. Tinnitus may be the first auditory symptom, affecting

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approximately 27–38% of adult patients. High incidence of otological symptoms and documented hearing loss have been reported, both in hemizygous males and heterozygous females (Germain et al., 2002; MacDermot et al., 2001; Conti and Sergi, 2003; Barras and Maire, 2006; Hegemann et al., 2006). Most patients develop progressive and accelerated sensorineural hearing loss, mainly in high frequencies, during adulthood. However, sudden deafness has also been reported (Germain et al., 2002; Barras and Maire, 2006). Germain et al. investigated the cochlear function in 22 hemizygous males with classic FD and reported a 54.5% prevalence of abnormal hearing and a high prevalence of sudden deafness. Interestingly, 33% of asymptomatic patients also presented high-frequency hearing loss on pure-tone audiometry (Germain et al., 2002). Vestibular disorders as vertigo, dizziness and chronic instability have also been reported in FD (Barras and Maire, 2006).

The incidence of otological symptoms appears to be increased in patients with renal failure or cerebrovascular involvement. On the other hand, there is no documented correlation between otological symptoms and left ventricular impairment (Germain et al., 2002). However, more studies are needed to clarify the preditors of inner ear involvement.

Enzyme replacement therapy (ERT), with alfa or beta-agalsidase, has demonstrated to promote clearance of GB3 deposits, stabilization or delay of the progression of renal failure, improvement of left ventricular hypertrophy and function and improvement of pain and quality of life (Breunig et al., 2003). ERT also appears to reduce vertigo and dizziness (Breunig et al., 2003; Mignani et al., 2004). Hajioff et al. found that ERT stabilized or slightly improved hearing function (Hajioff et al., 2006).

This study aims to evaluate cochleo-vestibular symptoms and characterize the hearing function in a large cohort of patients affected with FD followed in a reference centre of lysosomal storage disorders. We also aim to evaluate the factors associated to hearing loss and the effect of ERT in the cochleo-vestibular symptoms and hearing function.

2. Material and methods

This study included patients with confirmed diagnosis of FD, followed in a Reference Centre of Lysosomal Storage Disorders in the North of Portugal. FD diagnosis was based on the finding of a pathogenic GLA gene mutation in all patients (Table 1).

A detailed history was obtained with regard to otological symptoms, previous surgery or trauma, inherited deafness, exposure to ototoxic agents and acoustic trauma. All patients underwent otoscopy and vestibular clinical examination. Audiological evaluation consisted of pure tone air and bone conduction audiometry (with masking as appropriate), speech audiometry and middle-ear immitance testing (tympanometry and acoustic reflex testing). Audiological tests were performed and evaluated according to standard procedures (Katz, 2002). The type of hearing loss was divided as sensorineural, conductive or mixed. Pure tone average (PTA) was calculated using 500, 1000 and 2000 Hz frequencies. High frequencies - pure tone average (HF-PTA) at 4000 and 8000 Hz was also considered to better evaluate inner ear involvement. For each subject, impairment was classified according to the more affected ear. The degree of hearing loss was classified in mild (> 25 to ≤40 dB HL), moderate (> 40 to ≤55 dB HL), moderately severe (> 55 to ≤70 dB HL), severe (> 70 to ≤90 dB HL) and profound (> 90 dB HL) (Mazzoli et al., 2003). Hearing loss was considered in accordance with the age and gender-specific reference values published in literature (Morrell et al., 1996; International Organization for Standardization, 1984; Ries et al., 2007). Suprathreshold word recognition ability for phonetically balanced monosyllabic words was reported as percent correct. Word-recognition score above 88% was considered as normal, between 60 and 88% as suggestive of cochlear lesion and below 60% as indicative of retrocochlear pathology (Sergi et al., 2010). Middle ear pressure was quantified by tympanometry. Both ipsilateral and contralateral acoustic reflexes were measured.

Patients treated with ERT underwent an audiological evaluation before and 1 year after the beginning of the treatment. ERT with alfa-agalsidase (Replagal, Shire Human Genetic Therapies, MA, USA) was infused, every 2 weeks, at a dose of 0.2 mg/kg of body weight; and beta-agalsidase (Fabrazyme, Genzyme Corporation, Cambridge, MA, USA) was infused, every 2 weeks, at a dose of 1 mg/kg of body weight.

This study was approved by the Ethics Committee and an informed consent was obtained from all patients participating in this study. Statistical analysis was performed using SPSS Statistics 20.0®. A p value less than 0.05 was considered statistically significant.

Table 1
Pathogenic GLA gene mutations of the FD patients.

GLA gene mutations	n (%)	Phenotype
p.F113L	109 (89.3)	Later-onset
p.E203X	9 (7.4)	Classical
p.M290I	2 (1.6)	Classical
p.C94S	2 (1.6)	Classical

3. Results

A total of 122 patients with FD, 59 (48.3%) males and 63 (51.6%) females, were included in this study. Mean age was 47.1 ± 17.6 years, ranging from 5 to 89 years old. Overall otological complains were reported by 34.4% of the patients (Table 2). Hearing was considered normal by 90 patients (73.8%) and abnormal by 32 patients (26.2%), with a mean age of 43.5 ± 17.5 and 58.2 ± 14.2 years respectively (p = .001). Progressive hearing loss was reported by 30 patients (24.6%) (22 cases bilaterally and 8 cases unilaterally) and unilateral sudden deafness was reported by 2 patients (1.6%). Hearing loss complain was significantly more frequent in men (33.8% vs. 19.0%; p = .023). Tinnitus were mentioned by 28 patients (23.0%), without gender preference (p = .843), being associated with hearing loss in 17 cases. Tinnitus was unilateral in 8 patients, without side predominance. History of continued noise exposure was reported by 21 patients (17.2%) and 9 of those reported hearing loss and 5 patients with abnormal audiogram. Two patients had previous exposure to ototoxic agents (gentamicin and cisplatin) and they also reported hearing loss, confirmed on audiometry (Table 3). We found higher frequency of tinnitus in patients with diagnosis of depression (75.0% vs. 18.2%; p = .001).

Regarding pure tone audiometry, 75 patients (61.5%) presented a strictly normal audiogram, with a mean age of 40.2 ± 16.1 years. Sensorineural hearing loss was detected in 45 cases (36.9%), with a mean age of 59.8 ± 14.1 years (p = .001), ranging from 29 to 89 years, and this hearing loss was bilateral in 41 of those cases (91%). Unilateral conductive hearing loss due to chronic otitis media was found in 2 cases (1.6%).

Sensorineural hearing loss specially affected high frequencies. It was restricted to 4000 and 8000 Hz in 39 patients (32.0%). The 6 patients with low and middle frequencies (500, 1000 and 2000 Hz) impairment (4.9%) also presented high frequencies involvement. In these 6 patients,

Table 2
Characteristics of FD patients.

	All patients	Males	Females	*p*
n (%)	122 (100)	59 (48.3)	63 (51.6)	
Age (mean ± SD, years)	47.1 ± 17.6	47.8 ± 18.4	46.5 ± 16.8	.699
Otological complaints (%)	42 (34.4)	25 (20.5)	17 (13.9)	**.040**
ERT (%)	41 (33.6)	31 (25.4)	10 (8.2)	**.001**

p, Males vs. Females.
Bold - statistically significant.