European Annals of Otorhinolaryngology, Head and Neck diseases 136 (2019) 273–279

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Original article

Cochleovestibular manifestations in Fabry disease: Importance of screening and systematic ENT evaluation

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ARTICLE INFO

Keywords:
Fabry disease
Inner ear
Cochlear disease
Sensorineural hearing loss
Vestibular disease

ABSTRACT

Objectives: Fabry disease (FD) is an X-linked inherited lysosomal storage disease. It is a multisystem pathology that can include ENT disorders. The aim of the present study was to investigate the cochleovestibular manifestations of FD, in order to show the importance of screening and systematic ENT evaluation.
Material and methods: A single-center retrospective study included 14 male and 23 female FD patients. Hearing impairment was defined as hearing loss greater than the 90th percentile for at least one frequency. Vestibular impairment was defined by lateral semicircular canal dysfunction. Age, ongoing enzyme replacement therapy (ERT) and organic (renal, cardiac and cerebrovascular) complications were used as severity markers.
Results: Hearing impairment was found in 62.6% of cases, mostly at high frequencies, and was associated with age, ERT, and cardiac and cerebrovascular disorder. It affected 46.7% of asymptomatic adult patients. Vestibular impairment was found in 56% of cases, associated with age; it affected two-thirds of ERT patients, more than 60% of patients with organic complications, and 50% of asymptomatic adult patients.
Conclusions: More than half of patients had ENT involvement. All FD patients should undergo early ENT screening for diagnostic, prognostic and therapeutic purposes. Systematic complete ENT follow-up with auditory and vestibular evaluation should be performed regularly, even for heterozygous women.

1. Introduction

Fabry disease (FD) is an inherited X-linked metabolic disease, with incidence between 1/40,000 and 1/117,000 [1]. Deficient or absent alpha-galactosidase A (AGAL) activity leads to lysosome storage of glycosphingolipids (mainly globotriaosylceramide), causing multi-system disorders: acroparesthesia of the limbs, sudation disorder with effort intolerance, gastro-intestinal disorder, cutaneous angiokeratoma, and ocular and cochleovestibular involvement. Severity is related to renal, cardiac and cerebrovascular complications that can be life-threatening. Hemizygous males are affected earlier and more severely than heterozygous females, who transmit the disease, with variable impact due to X-chromosome deactivation. The reference treatment is enzyme replacement therapy (ERT).

Auditory impact has been reported for some 15 years, consisting in progressive sensorineural hearing loss predominating at high frequencies, with episodic sudden deafness that is more frequent than in the general population [2,3]. Vestibular impact has been little studied, with rates varying between 25% and 80% according to the report [4–6].

The main aim of the present study was to investigate cochleovestibular manifestations in FD. The secondary objective was to assess the correlation between cochleovestibular manifestations and disease severity, in order to show the importance of screening and systematic, complete and regular ENT assessment.

2. Material and Methods

A single-center retrospective study included all patients managed in our department with FD confirmed on genetic screening or AGAL enzymatic activity assessment: 16 male, 24 female. Thirty-seven underwent auditory assessment; 3 were excluded as having other clear cause of hearing impairment (1 history of surgically treated cholesteatoma, 2 cases of post-viral otitis media with effusion). Twenty-five underwent vestibular assessment. Age, ongoing

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https://doi.org/10.1016/j.anorl.2019.04.014
1879-7296/

Table 1
Audiometric analyses per ear and per patient (on poorer ear).

Analysis	By ear ($n = 74$)			By patient ($n = 37$)		
	All	Male ($n = 28$)	Female ($n = 46$)	All	Male ($n = 14$)	Female ($n = 23$)
MHL > 20 dB	23 (31.1%)	5 (17.9%)	18 (39.1%)	15 (40.5%)	4 (28.6%)	11 (47.8%)
Mild	16	5	11	10	4	6
Moderate	7	0	7	5	0	5
Severe	0	0	0	0	0	0
Profound	0	0	0	0	0	0
Total	0	0	0	0	0	0
HF MHL > 20 dB	36 (48.6%)	12 (42.9%)	24 (52.2%)	22 (59.5%)	7 (50%)	15 (65.2%)
Mild	14	4	10	9	2	7
Moderate	16	6	10	10	4	6
Severe	4	1	3	1	0	1
Profound	2	1	1	2	1	1
Total	0	0	0	0	0	0
Type of hearing loss	23	5	18	15	4	11
Sensorineural	22	5	17	14	4	10
Conduction	0	0	0	0	0	0
Mixed	1	0	1	1	0	1
Configuration	23	5	18	15	4	11
Ascending	0	0	0	0	0	0
U-shaped	2	0	2	2	0	2
Descending (shallow slope)	10	2	8	6	2	4
Descending (steep slope)	8	3	5	6	2	4
Flat	3	0	3	1	0	1

ERT and organic (renal, cardiac or cerebrovascular) complications were used as severity markers.

Hearing loss, tinnitus and episodic sudden deafness were screened for. Pure-tone audiometry was conducted in a sound-proof booth on a calibrated audiometer. Hearing impairment was classified according to International Bureau for Audiophonology guidelines, per ear and then per patient (in the poorer ear), on mean hearing loss (MHL: hearing loss at 500 + 1,000 + 2,000 + 4,000 Hz/4), as: normal (< 20 dB), mild (21–40 dB), moderate (41–70 dB), severe (71–90 dB) or profound (> 90 dB). High-frequency MHL (HF MHL) was calculated by averaging hearing loss between 4,000 and 8,000 Hz. Following European Working Group on Genetics of Hearing Impairment guidelines, MHL was categorized as sensorineural, conduction or mixed, and each audiogram was classified as ascending from low frequencies, U-shaped at middle frequencies, slightly or strongly descending at high frequencies, or flat [7]. Hearing loss was attributed to FD, after correction for age and gender, by comparing hearing thresholds in each ear against the 50th and 90th percentiles for a normal-hearing population according to ISO 7029–2017 at 250 to 8,000 Hz; auditory involvement was defined as hearing loss exceeding the 90th percentile on at least 1 frequency between 250 and 8,000 Hz and exceeding 20 dB (normal threshold value) in the poorer ear.

Recent or longstanding rotational vertigo or instability were screened for on videonystagmoscopy and videonystagmography (VNG) comprising rotational test seated (amortized rotation test) and caloric test with irrigation of each ear with cold water (30 °C) then warm water (44 °C) for 20 seconds. Vestibular involvement was defined as lateral semicircular canal involvement: directional predominance on rotational test (reproducible > 2°/s response asymmetry) and/or hypovalence (> 15% relative interaural deficit on Jongkees' formula) or hyporeflexia (sum of cold and warm water responses < 6°/s) on caloric test [8].

Renal involvement is defined as proteinuria > 0.3 g/24 h and/or glomerular filtration rate (GFR) < 60 ml/min/1.73m^2 [9]. Cardiac involvement is defined by left ventricle hypertrophy (LVH) on ultrasound or MRI, FD-typical myocardial fibrosis areas on MRI, or arrhythmia or cardiac conduction disorder (short PR interval) [1,9]. Cerebrovascular involvement is defined by history of transient ischemic attack (TIA) or stroke and/or gaps or hypersignal zones in periventricular white matter on MRI [2,9].

Chi^2 or Fisher exact test, as appropriate, and Student *t* test were used to assess associations, respectively, between two types of involvement and between one type of involvement and quantitative variables.

3. Results

Thirty seven patients (23 female (62.2%), 14 male (37.8%) were seen in ENT consultation between January 2007 and June 2017. Mean age was 40 years (range, 6–77 years), with 33 adults and 4 (male) children. Mean age was 47.6 years in females versus 27.4 years in males (or 34.7 years excluding children under 18 years of age). Twenty one patients (56.8%) received ERT (11 female, 10 male including 1 child), for a mean 54.4 months' treatment.

Fourteen patients (37.8%) reported hearing impairment, and 14 reported tinnitus, associated in 10 cases. Four reported an episode of sudden deafness (12% of adults): 1 unilateral and 3 implicating pressure (fluctuating low-frequency hearing loss with associated dizziness). Half of the adults (18 patients: 54.5%) showed some auditory symptomatology: hearing impairment, tinnitus or sudden deafness. Table 1 presents audiometry results. Thirty seven of the 74 tested ears had hearing threshold > 20 dB and > 90th percentile on at least 1 frequency (Fig. 1). Hearing loss was predominantly in the 4,000–8,000 Hz range (Fig. 2), and concerned 23 of the 37 patients (69.7% of adults: 17/23 women (73.9%) and 6/10 adult men. Hearing loss was found in 7 of the 15 adults without auditory complaint (46.7%). Children were all asymptomatic, with normal hearing.

Twenty five patients underwent instrumental vestibular assessment: 18 female, 6 male (including 1 child): mean age, 44.7 years. Fifteen of the 25 (60%) reported recent vestibular symptoms (8 cases of rotational vertigo and 11 of instability), and 18 reported history of rotational vertigo and/or instability. Seven patients without vestibular symptoms (including the child) had systematic assessment. Table 2 presents results. Lateral canal involvement was found in 14 patients: 11 females, 3 adult males. Vestibular involvement was found in 4 of the 9 adults (44.4%) without symptoms

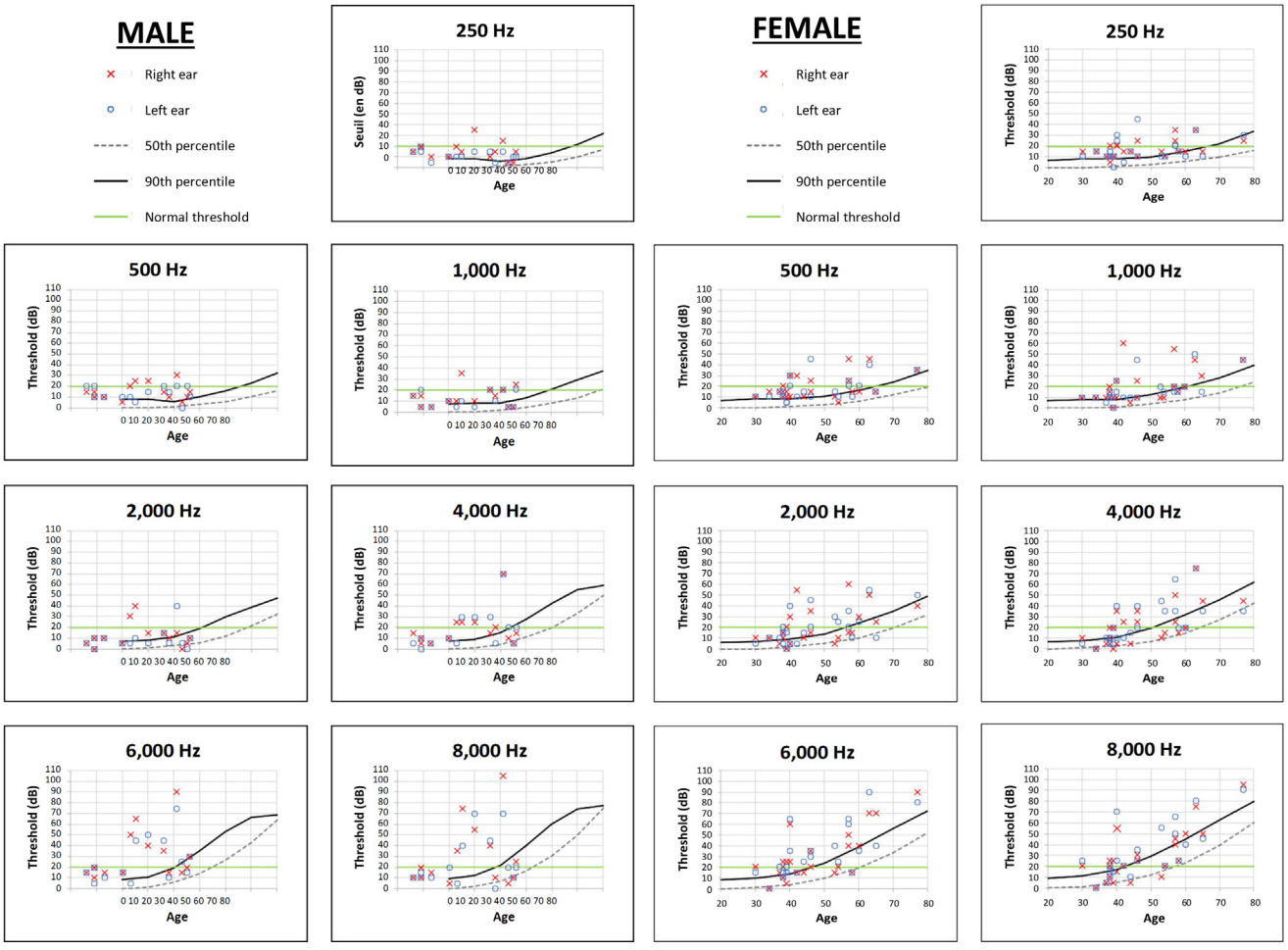

Fig. 1. Hearing loss per frequency corrected on age and gender in comparison to 90th and 50th percentiles for normal-hearing population according to ISO 7029–2017.

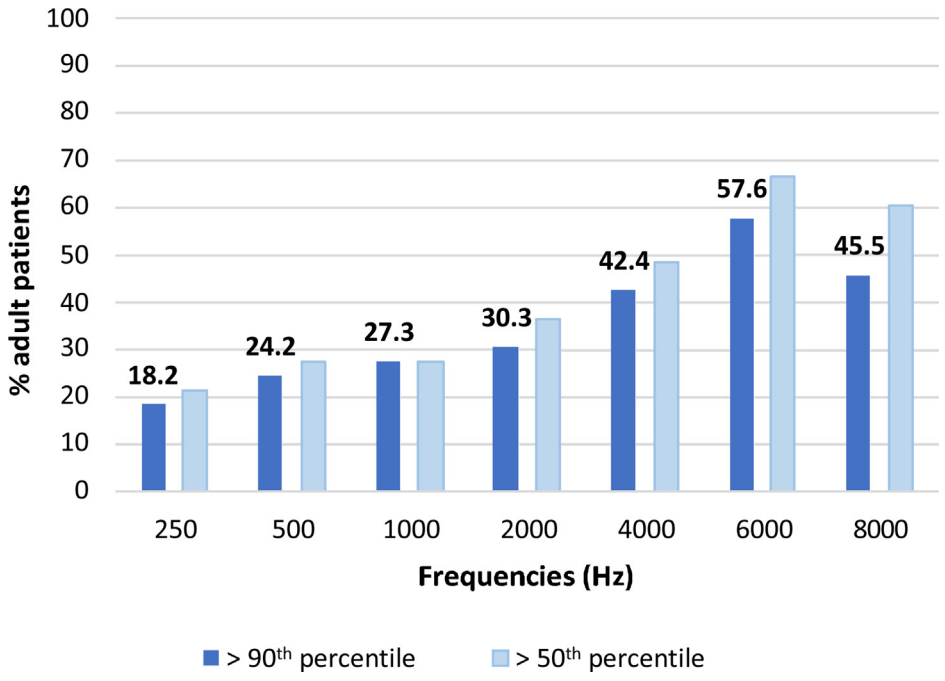

Fig. 2. Percentage of adult patients with hearing threshold > 20 dB and above 90th and 50th percentiles at 250–8,000 Hz.

Table 2
Vestibular exploration results in 25 tested patients.

Patient nº	Gender	Age	ERT	Symptoms			VNS				VNG								Lateral canal vestibular involvement
				RV	Instability	History of RV and/or I	BPPV	Positional *n*	HST	Spontaneous *n*	Seated		Caloric test						
											DP	Side	RE	H or AR	LE	H or AR	Hypo valence	Side (%)	
1	F	54									+	L	14.3		13,3				+
2	M	20	+										17.8		13,6				
3	F	46	+								+	L	33.5		33,1				+
4	M	13	+										17.4		14,1				
5	F	39		+		+							57.7		57,8				
6	M	41	+	+	+	+				+ (excl. G)	+	L	25.4		23,1				+
7	F	63	+	+	+	+			+		+	L	3.8	+	1,2	+	+	L (52)	+
8	F	44											13		14,6				
9	F	60	+		+	+					+	L	16.8		8,4		+	L (33)	+
10	F	39	+		+	+							11.7		6,1		+	L (32)	+
11	F	34				+							34		37,2				
12	F	38									+	L	23.8		30,5				+
13	F	58	+			+							13.1		12,6				
14	F	77			+	+							7.9		41,8		+	R (68)	+
15	M	45	+		+	+							71		17		+	L (61)	+
16	M	43	+		+	+					+	R	30.1		28,7				+
17	F	40		+		+							15.3		16,1				
18	F	57	+	+		+	+						12.8		14,3				
19	M	36	+	+	+	+							6.7		6				
20	F	38											24.8		25,7				
21	F	42	+	+	+	+		+		+			12.5		5,3	+	+	L (41)	+
22	F	57	+			+				+			23.7		3,7	+	+	L (73)	+
23	F	65	+		+	+				+			16.5		0	+	+	L (100)	+
24	F	30		+		+					+	R	8.4		13,9		+	R (24)	+
25	F	38			+	+							15.5		15,4				
Total			15	8	11	18	1	1	4	1	8		1			4	9		14

F: Female; M: Male; ERT: Enzyme replacement therapy; RV: Rotational vertigo; N: Nystagmus; VNS: Videonystagmoscopy; BPPV: Benign paroxysmal positional vertigo; HST: Head-shaking test; VNG: Videonystagmography; DP: Directional preponderance; LE: Left ear; RE: right ear; H or AR: Hypo- or areflexia.

on examination and in 50% of adults without history of vertigo or instability.

Eleven of the 25 patients (44%) had both auditory and vestibular involvement, although the two did not correlate.

No children showed organic complications, while 78.8% of adults (19 female, 82.6%; 7 males, 70%) presented at least 1. Eight showed renal involvement (24.2% of adults: 7 female, 1 male): 3 cases of isolated proteinuria, 1 of moderate kidney failure, 1 of terminal kidney failure, 2 with dialysis and 1 with transplant. More than half the adults (54.5%: 13 female, 5 male) showed cardiac involvement: 12 cases of LVH and/or cardiac fibrosis on MRI, 7 of conduction disorder, including 1 with pacemaker, and 3 with arrhythmia (involvement was in some cases multiple). 51.5% of adults (11 female, 6 male) showed cerebrovascular involvement: 4 cases of history of stroke, 2 of history of TIA, 2 with subclinical gaps on MRI, and 9 with multiple white matter hypersignal. Females showed more renal (30.4% versus 7.1% in males), cardiac (56.5% versus 35.7%) and cerebrovascular (47.8% versus 42.9%) complications.

Table 3 shows associations between audiovestibular involvement and FD severity markers. Subjects with auditory involvement had a significantly greater mean age, more cardiac and cerebrovascular complications and more frequent ERT. No correlation emerged between hearing and renal involvement, although 75% of the 8 patients concerned showed hearing loss. Subjects with episodic sudden deafness more often had history of stroke and/or TIA and/or MRI gaps ($P = 0.03$). Subjects with vestibular involvement had a significantly greater mean age. Two-thirds of those treated had lateral canal deficit, although the association was not statistically significant. There was no significant association between lateral canal deficit and organic complications, although vestibular involvement was found in 60% of patients with renal involvement, 61.5% of those with cardiac involvement and 71.4% of those with cerebrovascular involvement.

In total, 91.3% of patients with impaired hearing had some kind of organic involvement, and 80.8% of those with organic involvement had hearing impairment. In total, 92.9% of patients with vestibular involvement had some kind of organic involvement, and 65% of those with organic involvement showed lateral canal deficit.

Isolated auditory and vestibular ENT involvement was found in one 38 year-old asymptomatic female without ERT or organic complications.

4. Discussion

62.6% of the present cases showed auditory involvement. There were 4 cases of sudden deafness: i.e., 12% of adults. Incidence of sudden deafness is known to be greater in FD patients than in the general population, ranging from 12% to 35%, although the hearing loss is not severe and prognosis for recovery is good [2,10–12]. Auditory involvement in FD was assessed in series ranging between some twenty to some hundred patients, with heterogeneous and unclear definitions [2–4,10,13–15]. Authors agreed on the likely endocochlear origin of the deafness and its high-frequency predominance, confirming the present findings: sensorineural hearing loss (93%) descending toward high frequencies (80%) in 40% of patients in the poorer ear, or in 60% considering only high frequencies [2,10,13,15]. In the present study, females were more severely affected than males, perhaps due to an age difference: mean 47.6 years in females versus 27.4 years in males. To implicate FD in hearing loss, data were corrected for age and gender [16]. Three patients were excluded as having other causes of hearing loss. Other factors may have been overlooked, as relevant data were not collected: familial history, ototoxicity, trauma. Almost two-thirds of adult males showed hearing thresholds exceeding 20 dB and the ISO 90th percentile on at least 1 frequency, mainly between 4,000 and 8,000 Hz, in agreement with other studies based on the 90th percentile (60% for Sakurai et al.) or 95th percentile (79% for Hegemann et al., and 55% for Ries et al.) [3,11,14].

Fifty-six% of cases showed lateral canal deficit: 57.9% of females and 60% of adult males. Fifteen patients (60%) reported recent episodes of rotational vertigo or instability; 4 of these had normal VNG. One female patient (n^o 18) showed benign paroxysmal positional vertigo due to right posterior canalolithiasis, reduced before VGN. Central etiology was suspected in patient n^o 14 in view of well-compensated right hypovalence associated with impaired ocular fixation fraction, and in patient n^o 15, in view of right hyper-reflectivity. In the other 8 patients, hydrops was diagnosed: patient n^o 6 was in acute phase, with spontaneous left horizontal nystagmus; in the other 7, diagnosis was multifactorial. Four of the 10 asymptomatic patients showed abnormalities on VNG: isolated directional preponderance in seated posture in 3 cases, and 1 patient with history of left vestibular neuritis with left hypovalence. Vestibular involvement data could not be corrected on age and gender. In the literature, rates of lateral canal deficit on caloric test range from 8% to 50% in samples of around 20 patients, with varying criteria (relative interaural deficit thresholds ranging between 25% and 40%) or criteria not specified [4,5,10,13,17]. The head-shaking test (HST) was used by Palla's team: at least 1 of the 6 canals was involved in 80% of males and 77% of females, compared to respectively 21% and 0 on caloric test, suggesting that HST is more sensitive in detecting vestibular deficit in FD, as symmetric bilateral involvement is not picked up by the caloric test [4,18]. Predominantly high-frequency involvement has also been hypothesized, as all patients with pathologic caloric test results show involvement on HST whereas the converse does not hold. To assess vestibular involvement in FD more precisely, it would be interesting to assess results on video-HST and evoked myogenic potentials (cVEMP, oVEMP).

Auditory involvement is rare in children, all of whom were free of ENT symptoms and involvement in the present series, and tinnitus is an early symptom, especially in case of associated organ involvement [19,20].

ENT screening should be systematic, as almost half of asymptomatic adults (46.7%) show hearing loss attributable to FD, mainly on high frequencies, as also reported by Germain et al., and 50% of asymptomatic adults show lateral canal involvement [2]. That symptoms do not correlate with vestibular involvement is because deficit is mainly symmetrically bilateral with slow progression, allowing compensatory mechanisms to develop [6,10].

Age correlated with auditory and vestibular involvement, in agreement with Palla et al. [4]. ERT was associated with auditory involvement, and two-thirds or treated patients showed vestibular involvement.

Organ involvement was frequently associated with vestibular involvement: in 60% of cases for renal, 61.5% for cardiac and 71% for cerebrovascular complications. This association was never previously analyzed.

In the present series, auditory involvement was associated with cardiac ($P = 0.01$) and cerebrovascular involvement ($P = 0.02$), in agreement with previous reports: 100% of patients with cerebrovascular involvement and 80% with cardiac involvement showed hearing impairment according to Pichon et al. In 2002, Germain et al. reported a correlation between hearing loss and cerebrovascular involvement (MHL 50.7 dB with versus 14.9 dB without cerebrovascular involvement) and a considerable difference in MHL between the groups with (40.3 dB) and without LVH (23.4 dB). Hearing loss was also associated with proprioceptive deficit and white matter lesions according to Ries et al. [2,10,11]. Three-quarters of the present series with renal involvement showed

Table 3
Contingency tables between audio-vestibular involvement and FD severity markers: age, ERT and organic complications.

ENT involvement	Age		ERT			Organic complications								
						Renal			Cardiac			Cerebrovascular		
	Mean age	*P*	+	–	*P*	+	–	*P*	+	–	*P*	+	–	*P*
			n = 21	*n* = 16		*n* = 8	*n* = 29		*n* = 18	*n* = 19		*n* = 17	*n* = 20	
Auditory														
+ (*n* = 23)	46.1	0.002[a]	16	7	0.04[b]	6	17	0.68[c]	15	8	0.01[b]	14	9	0.02[b]
– (*n* = 14)	29.9		5	9		2	12		3	11		3	11	
	Mean age	*P*	+	–	*P*	+	–	*P*	+	–	*P*	+	–	*P*
			n = 15	*n* = 10		*n* = 5	*n* = 20		*n* = 13	*n* = 12		*n* = 14	*n* = 11	
Vestibular														
+ (*n* = 14)	50	0.03[a]	10	4	0.24[c]	3	11	1[c]	8	6	0.56[b]	10	4	0.08[b]
– (*n* = 11)	37.9		5	6		2	9		5	6		4	7	

[a] Student test, [b]Chi[2] test, [c]Fisher exact test.

auditory involvement, although no significant correlation could be demonstrated, probably due to lack of power. An association between the kidney and hearing loss has been frequently reported, but only Ries et al. found a significant association between renal function and hearing loss corrected against the 95th percentile [2,10,11,14]. In a multivariate analysis including 108 patients, hearing loss predicted organic complications, with relative risk of cerebrovascular, cardiac and renal involvement of respectively 3.1, 3.2 and 3.9, whence the interest of early assessment [9]. More than 90% of patients with ENT involvement have at least one serious organic involvement: ENT involvements must therefore be screened for in case of organ involvement, and vice-versa.

ERT should be initiated early, before fibrosis and cell death set in [1], and should be implemented in all adult males, even if asymptomatic, and in highly symptomatic women and children, although it should not be systematic in women and children with few or no symptoms [1,21]. In the present study, 1 non-treated female without organ lesion or ENT symptomatology presented auditory and vestibular involvement. Screening for subclinical involvement (notably auditory, given the association with organic complications) could be one indication for ERT in women and children [5,9].

Males generally show more frequent and more severe auditory and vestibular involvement than females [3,4,14,15]. In the present series, however, females were affected as much as or more than males: 58% of women and 60% of adult men showed vestibular involvement, and 73.9% and 60% respectively showed auditory involvement, even after correction for gender. This may have been due to inequalities in the distribution of the more numerous female sample, which was older and showed more organic complications. The present results confirmed that women were indeed affected, despite their heterozygosity; women as much as men should therefore be assessed and monitored.

The pathophysiology of ENT lesions in FD is controversial. In cochlear involvement, a vascular mechanism with Gb3 deposition in the upstream arteriolar vascular endothelium is thought to predominate, whereas vestibular involvement would be due to direct injury [10,22]. This would account for the lack of interrelation between the two, in the present study and in the literature [4,6,13]. ENT work-up should be exhaustive, including audiometry and complete vestibular examination in VNG and, if possible, video-HST with otolithic exploration. Annual ENT assessment may be proposed [11]. Sensory deficits should be managed promptly, with auditory and vestibular rehabilitation, as, although not life-threatening, they have negative impact on quality of life [15].

5. Conclusion

More than half (62.2%) of the present FD patients showed hearing impairment, in the form of sensorineural hearing loss predominating at high frequencies, or vestibular involvement (56%), in the form of lateral canal deficit.

Early screening is recommended:

- for diagnostic purposes, as ENT involvement may be asymptomatic;
- for prognostic purposes, as ENT lesions are associated with FD severity;
- for therapeutic purposes, as ERT may be indicated.

All FD patients should have regular complete auditory and vestibular work-up, given the frequency of ENT involvement, especially in severe FD (advanced age or organic complications). Heterozygous females should be monitored just as much as hemizygous males. Cardiac, renal and cerebrovascular complications should be screened for in case of hearing loss or vestibular deficit, and vice versa. Early management of hearing loss or vestibular deficit is indispensable: although not life-threatening, sensory impairment has negative impact on quality of life.

Disclosure of Interest

The authors declare that they have no conflict of interest.

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