Neuro-otological and peripheral nerve involvement in Fabry disease

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Abstract

Fabry disease (FD) is an X-linked lysosomal storage disease, with multisystemic glycosphingolipids deposits. Neuro-otological involvement leading to hearing loss and vestibular dysfunctions has been described, but there is limited information about the frequency, site of lesion, or the relationship with peripheral neuropathy. The aim was to evaluate the presence of auditory and vestibular symptoms, and assess neurophysiological involvement of the VIII cranial nerve, correlating these findings with clinical and neurophysiological features of peripheral neuropathy. We studied 36 patients with FD with a complete neurological and neuro-otological evaluation including nerve conduction studies, quantitative sensory testing (to evaluate small fiber by warm and cold threshold detection and cold and heat pain), vestibular evoked myogenic potentials, videonistagmography, audiometry and brainstem auditory evoked potentials. Neuro-otologic symptoms included hearing loss (22.2%), vertigo (27.8%) or both (25%). An involvement of either cochlear or vestibular function was identified in most patients (75%). In 70% of our patients the involvement of both cochlear and vestibular function could not be explained by a neural or vascular mechanism. Small fiber neuropathy was identified in 77.7%. There were no significant associations between neuro-otological and QST abnormalities. Neuro-otologic involvement is frequent and most likely under-recognized in patients with FD. It lacks a specific neural or vascular pattern, suggesting multi-systemic, end organ damage. Small fiber neuropathy is an earlier manifestation of FD, but there is no correlation between the development of neuropathy and neuro-otological abnormalities.

Introduction

Fabry disease (FD) is an X-linked lysosomal storage disease caused by inherited deficiency of α-galactosidase A, a lysosomal enzyme. The resultant inability to catabolize glycosphingolipids[1] causes progressive multi-systemic accumulation of globotriaosylceramide and globotriaosylsphingosine.[2] Multisystemic glycosphingolipids deposits lead to intracellular accumulation predominantly in the vascular tissue, eye, skin, kidney, heart and nervous system.[3]

The estimated prevalence has varied between 1:40,000 and 1:117,000 live births.[4,5] When later-onset variant phenotypes are included the incidence ranges from 1:31,000 to 1:4600.[6] Clinical manifestations frequently begin in childhood, with neuropathic pain, hypohydrosis, angiokeratomas, gastrointestinal symptoms, such as abdominal pain and diarrhea, and cornea verticillata. Most untreated males usually die within the fifth decade of life.[7] Although females may experience milder symptoms, their life expectancy is also reduced by about 15 years compared with the unaffected population.[8] The long delay between the onset of symptoms in FD and the correct diagnosis is likely due to the poor recognition of the clinical manifestations.[9,10] The causes of premature death are renal failure, cardiomyopathy and cerebrovascular disease.[11]

Recently, enzyme replacement therapy (ERT) with gene-activated human α-Gal A provided evidence of stabilizing or improving several clinical manifestations.[2,12] ERT has proven to be safe and effective, and it is most useful when administered early in the course of the disorder.[13,14]

Neuro-otological involvement leading to hearing loss and vestibular dysfunctions has been described in FD;[15,16] but there is limited information about the frequency, site of lesion, or the relationship with peripheral neuropathy.

Objectives

The aim was to evaluate the presence of auditory and vestibular symptoms in our patients and to assess neurophysiological involvement of the cochlear, superior and inferior vestibular branches of the VIII cranial nerves. In addition, we were interested in evaluating the clinical and neurophysiological features of peripheral neuropathy, and correlate these findings with the presence of neuro-otological abnormalities.

Materials and Methods

We studied 46 consecutive patients with FD, diagnosed by enzyme assay or DNA analysis, during the years 2007-2012. We

excluded 3 diabetic and 7 pediatric patients. The remaining group included 36 patients (11 males, mean age 34.7 years old, range 18-60; 25 females, mean age 36.1 years old, range 18-73). In every patient we performed a complete neurological and neuro-otological evaluation, including nerve conduction studies (NCS), quantitative sensory testing (QST), vestibular evoked myogenic potentials (VEMP), videonistagmography (VNG), audiometry and brainstem auditory evoked potentials (BERA). Patients with conductive hearing loss were excluded.

Neuro-otological evaluation

VNG (Fireware, Interacoustics, Denmark) included the study of saccadic eye movements, smooth pursuit and optokinetic nystagmus (OKN) and conventional caloric tests, wich we are considered abnormal when the asymmetry of SPV (Slow Phase Velocity) is over 25%. Auditory function was tested using conventional pure tone audiometry with speech discrimination, using conventional techniques. BERA were generated by a brief click at 90 dB normal hearing level nHL.

VEMP were recorded from the upper half of the contracted sternocleidomastoid muscle, using surface electrodes with a reference on the upper edge of the sternum. We stimulated ipsilaterally with rarefaction clicks, of 100-105 db, 0.1 ms duration and at a rate of 10 per second through a headphone.[17] We have taken as reference values the following: threshold 90-100 dBnHL, latency p1 15.91 msec (SD +/- 2), latency n1 23 msec (SD +/- 1.5), asymmetry in interaural amplitudes <35%.[17]

Neurological evaluation

NCS were performed using standard techniques in at least 2 motor (peroneal and median) and 2 sensory (sural and median) nerves in one leg and one arm. Compound motor action potentials amplitudes were measured from baseline to peak, and distal latencies to the onset of the response. Studies were performed with control of skin temperature (above 34°C), and care was taken to use just supramaximal percutaneous stimulation to avoid stimulation of adjacent nerves.

QST was performed by the method of Limits, using a Medoc TSA-2001 NeuroSensory Analyzer equipment. We evaluated different modalities including cold (CDT), warm (WDT), cold pain (CP) and heat pain (HP) detection thresholds in the dorso-medial region of the foot. The vibratory detection thresholds (VDT) were investigated in the first metatarsal head. Results were compared with those of a control group matched for age and gender using Mann-Whitney Rank Sum test.

Statistical analysis

We explored the association between the age of patients (<35 or ≥35 years) and neuro-otological abnormalities. A Chi-Square independence test was carried out for each variable *versus* QST, followed by Bonferroni correction test for P values.

Results

All patients presented symptoms or signs of FD (Table 1). Fourteen patients (38.8%) were under treatment with ERT, for a mean of 31.9 months.

Neuro-otological evaluation

In our group, 75% of patients reported either pure vertigo (10/36, 27.8%), pure hearing symptoms (8/36, 22.2%), or both

(9/36, 25%). Nine patients were asymptomatic. Five patients showed progressive hearing loss, and 12 referred tinnitus; no patient presented sudden hearing loss (Figure 1A).

42% have normal Pure Tone Audiograms. Scotomas in the frequency 2000 Hz was the most common finding in 44%, followed by high pitch hearing loss in 8% and profound hearing loss in 6% (Figure 1B)

We found 2 types of vertigo: brief and recurrent episodes of non positional vertigo lasting for minutes (11/36, 33%), and a second type of protracted crises lasting for hours or days (5/36, 13%).

VEMP, exploring the inferior division of the vestibular nerve, were abnormal in 45% of patients and VNG with caloric tests,

Table 1. Clinical manifestations in Fabry patients.

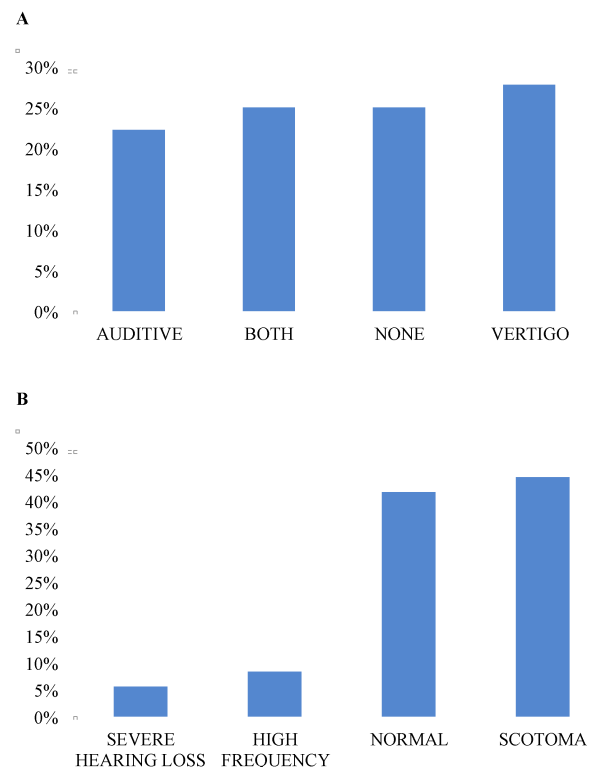| Symptom/Signs	Frequency (%)
Neuropathic pain	77.7
Cornea verticillata	75.8
Neuro-otological symptoms	75
Vertigo	27.8
Hearing loss	22.2
Both	25
Tinnitus	33%
Left ventricular hypertrophy	51.8
Angiokeratoma	50
Sweating dysfunction	44.4
Abdominal pain	44.4
Proteinuria	33.3

Figure 1. Neuro-otological manifestations. A) Neuro otological symptoms. B) Audiometry findings.

assessing the superior division of the vestibular nerve, were abnormal in 51%. Conventional audiometry diagnosed sensorineural hearing loss in 58% of patients. In patients with protracted vertigo crises, neuro-otological studies were always abnormal, and in the group with brief and recurrent crises the prevalence of abnormalities in VEMP and caloric tests was 77%. Hearing loss was sensorineural in all patients. High frequencies were affected first, and their severity ranged from isolated scotomas to severe hearing loss involving one or both ears. Only 25% of patients had completely normal neuro-otological/neurophysiological evaluation. There was not relationship between the age of the patients and the severity/hearing loss type.

BERA never showed a central pattern and reflected the expected changes produced by the hearing loss.

An involvement of both cochlear and vestibular function that could not be explained by a neural or vascular mechanism was identified in most patients (70%). They included cochlear involvement in one ear with contralateral superior or inferior vestibular dysfunction, or superior vestibular involvement in one side with inferior vestibular damage on the other. Therefore, the majority of our patients did not present a neural or a vascular distribution of their abnormalities (Figure 2), which is known as *no Pattern*.[18]

Neurological evaluation

NCS ruled out large fiber peripheral neuropathy in all patients, although 2 patients had carpal tunnel syndrome.

Abnormal QST was identified in 77.7% of patients (100% males and 47.2% females). In the affected subgroup, CDT was abnormal in 92.85%, followed by WDT and VDT (42.85%). Compared with the control group, female patients with FD presented significantly altered CDT (P<0.0001). In males, all modalities investigated, except CP, were significantly abnormal (Figure 3).

There was no significant association between neuro-otological abnormalities and age (P=0.73, Pearson Chi-Square, df=1). None of the tested variables were associated with QST abnormalities (P>0.05). The result for each pair of variables was as follows P value; Chi-square; degrees of freedom (df): BERA/QST P=0.42, X^2=1.75, df=2; VNG/QST P=0.37, X^2=0.81, df=1; Audio/QST P=0.22, X^2=1.5, df=1; VEMP/QST P=0.65, X^2=0.2, df=1.

Discussion

Hearing loss in FD is a frequent symptom, and it has been reported both in children[19] and adults.[19,20] Studies including pure tone audiometry identified hearing loss at both low and high frequencies, and noted that it was more frequent in older patients with renal and MRI abnormalities.[21] 33% of our patients, with or without hearing loss, had tinnitus. In our patients with hearing loss, low tones were overall more preserved than high ones, and involvement was in general asymmetric. Although sudden hearing loss have been reported as more prevalent in FD than in the general population,[21,22] none of our patients had this presentation.

We used different tests to explore each of the 3 divisions of the VIII cranial nerve, and we identified abnormalities even in asymptomatic patients, suggesting that both clinical and subclinical involvement are frequent in adult patients with FD. Abnormalities were more prevalent in older patients, although this difference was not statistically significant.

Previous reports addressed hearing loss almost exclusively. Our findings, underline that vestibular involvement is frequent and may be a disabling symptom in patients with FD.[20,23]

The location of vestibulo-cochlear damage in Fabry disease is not known. We found no vascular or neuropathic pattern to account for the neuro-otological findings, and there was no correlation between neuropathic and VIII nerve involvement. Therefore it is likely that the impairment is located at receptor level, within the vestibulo-cochlear laberynth, with a bilateral and asymmetric pattern. This agrees with histological findings in the temporal bones of two patients with FD which suggested that the etiology of cochlear lesions was due to a vascular damage of the hair cells induced by glycosphingolipid accumulation in the stria vascularis and in the spiral ganglion cells.[24] Moreover, other studies also suggested that the auditory deficits are due to a cochlear impairment.[20,25-27]

Neuropathic pain in FD is associated with small fiber neuropathy. The diagnosis of this type of neuropathy is based on symptoms: dysestesias, hypoesthesia and pain, as well as clinical signs such as abnormalities in both pin-prick and thermoalgesic sensation. QST and skin biopsy are used to confirm the diagnosis.[28] About 80% of Fabry patients suffer from painful neuropathy, which usually begins during the first two decades of life,[19,20] involving both soles and palms, and may present as crises with excruciating pain in hands and feet lasting from minutes to days.[19,21] Neuropathic pain may be either spontaneous or triggered by cold, heat, fever, exercise, stress or fatigue.[29-31] Pain may be so severe that sometimes leads to depression and suicidal ideation.[32-34] Small fiber neuropathy in patients with FD is length dependent.[35,36]

It is uncertain whether neuropathy arises from storage of lipids in dorsal root ganglia leading to a dying-back neuropathy, or from direct damage to small fibers. Pathophysiological hypothesis include the accumulation and abnormal distribution of sodium channels in injured axons, leading to increased mechanical excitability with repetitive nerve firing, pathological sympatho-
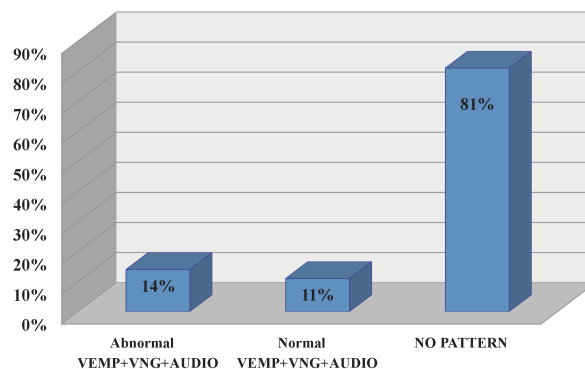

Figure 2. Distribution of neuro-otological manifestations; VEMP, vestibular evoked myogenic potential; VNG, videonystagmography; AUDIO, audiometry.

	Fabry patients (36) vs Controls P value	Fabry males (11) vs Controls P value	Fabry females (25) vs Controls P value
CDT	<0.001	<0.001	<0.001
WDT	<0.113	<0.001	0.79
CP	0.235	0.004	0.949
HP	0.879	0.001	0.046
VT	<0.008	0.001	0.102

Figure 3. Quantitative sensory testing in patients and controls. CDT, cold detection threshold; WDT, warm detection threshold; CP, cold pain threshold; HP, heat pain threshold; VT, vibration threshold.

afferent coupling, central or peripheral nociceptive sensitization, and even ischemia.[36-39]

QST studies explore non-invasively the function of small (myelinated and unmyelinated) and large myelinated fibers, as well as the receptor function. QST abnormalities may precede clinical findings,[40,41] but the results are not specific of peripheral nerve dysfunction, and the test requires patient's collaboration.[42]

In our group the majority of patients presented thermal threshold abnormalities in their QST studies. Moreover, CDT abnormalities in the feet was the most frequently affected parameter, suggesting a more pronounced pathology of the thinly myelinated fibers than the unmyelinated ones.[36,43,44]

Nerve conduction studies were normal in all our patients despite that some presented vibration thresholds abnormalities. Some[43,45,46] but not all[28,36,37,39,44] previous studies have also identified vibration abnormalities. It is likely that this finding is due to either more severe neuropathy, or vibratory receptors involvement because of intradermal GB3 deposits. Since large fiber peripheral neuropathy is not characteristic of FD, NCS should be normal in all patients. However, unlike our experience, Dutsch *et al*.[12] reported 30 patients with history of painful neuropathy of both hands and feet, and found that amplitudes of motor and sensory nerve action potential were significantly smaller than those of controls.

Despite X linked inheritance, heteroygous females have classical signs of the disease, and may be severely affected.[31,47,8] Nevertheless, the neuropathic symptoms in females with Fabry disease, together with the neurophysiologic evaluation , have not been extensively investigated. Studies that evaluated females as a group compared with controls have failed to identify significant abnormalities most likely because only half of them are affected,[35] but when QST is analyzed individually as we have shown, a large proportion of females present evidence of small fiber neuropathy.[28,44,48]

Finally, it is of outmost importance to underline that both neuro-otologic and peripheral manifestations of FD may respond to enzyme replacement treatment.[19,27,43,45,49,50]

Conclusions

Neuro-otologic involvement is frequent and under-recognized in patients with FD, it causes great disability, and affects both males and females. The site of lesion is probably located in the vestibular-cochlear labyrinth in the vast majority of the patients. There is no specific neural or vascular pattern, which is apparently a landmark of FD, suggesting multi-systemic damage. Inferior vestibular nerve evaluated by VEMP is frequently affected both in symptomatic and asymptomatic males and females with FD. Neuropathy in FD is a frequent finding, including in females that can be assessed non-invasively by QST but there is no correlation between neuropathy and neuro-otological abnormalities.

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