

## Otological aspects of Fabry disease in patients with normal hearing

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### ABSTRACT

We investigated the otological aspects of Fabry disease (FD) in patients with normal hearing. Forty-one patients (21 men, 20 women) with bilaterally normal hearing were recruited, and their otological symptoms and hearing evaluations, which included pure tone audiometry (PTA) and distortion product otoacoustic emission (DPOAE), were investigated. Ten of the 21 male (47.6%) and eight of the 20 female (40.0%) patients had otological symptoms, of which tinnitus was the most frequent. Cardiac dysfunction was more frequently observed in female patients. The average thresholds on PTA were below 25 dB at all frequencies, but DPOAE amplitudes were significantly lower in female patients at some frequencies. Otological symptoms were frequently observed in patients with FD, despite their normal hearing levels on PTA. DPOAE might provide useful information regarding cochlear disturbances related to the disease..

Keywords: Fabry disease; normal hearing; pure tone audiometry; otoacoustic emission

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### INTRODUCTION

Fabry disease (FD) is an X-linked inherited disorder of sphingolipid metabolism due to the deficient activity of lysosomal  $\alpha$ -galactosidase A,<sup>1</sup> occurring in between 1/117,000 and 1/476,000 live births.<sup>2</sup> This enzyme deficiency leads to the deposition of glycosphingolipids (mainly globotriaosylceramide (GL-3) and to a lesser extent galabiosylceramide) in the microvasculature and in various cell types of the kidneys, heart, and nervous system. The multisystemic nature of FD does not spare the cochleovestibular system, and hearing loss is a well-known feature of patients with FD. Symptomatic hearing loss was reported in 41% of hemizygous male and 23.3% of heterozygous female patients.<sup>3,4</sup> A temporal bone study in cases of FD with bilateral sensorineural hearing loss reported seropurulent effusions and hyperplastic mucosa in the middle ears, striae and spiral ligament atrophy in all turns, hair cell loss mainly in the basal turns,

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and reduced numbers of spiral ganglion cells in the cochlea.<sup>5</sup> Similar findings were reported in alpha-galactosidase A-deficient mice as a model of FD.<sup>6</sup>

There is a high incidence of inner ear involvement in FD, both in hemizygous male and heterozygous female patients,<sup>7</sup> but there are very few reports concerning the inner ear disturbances in an early stage before hearing deterioration, including otological symptoms. Distortion product otoacoustic emission (DPOAE) reflects an amplifier function of cochlear outer hair cells.<sup>8,9</sup> DPOAE is a non-invasive and objective method that has great frequency specificity with high reliability above 1000 Hz.<sup>10</sup> This study was designed to investigate the otological aspects of FD in patients with normal hearing.

## MATERIAL AND METHODS

A questionnaire about otological symptoms and auditory examinations for all patients with FD were administered as part of a medical screening test, and 45 patients (23 men, 22 women) referred to our department were included in the present study. Two male and one female patient with unilateral sensorineural deafness and one female patient with insufficient audiological data were excluded. Thus, the analysis included 42 ears of male and 40 ears of female patients. The diagnosis of FD was based on enzymatic assay of  $\alpha$ -galactosidase and  $\alpha$ -galactosidase gene sequencing. The patients' otological symptoms and other complications were documented from medical interviews and clinical charts.

Pure-tone audiometry (PTA) was performed using a diagnostic audiometer (AA-78; RION, Tokyo, Japan) in a soundproof room. Air conduction and bone conduction audiometric measurement thresholds were calculated for each ear at 250, 500, 1000, 2000, 4000, and 8000 kHz with a 5-dB step method. As a pre-selection criterion, normal hearing ears were defined as having normal eardrums, type A tympanograms, and normal audiograms (25 dB or better for 250, 500, 1000, 2000, 4000, and 8000 Hz). DPOAEs were measured using an analyzer (ILO292; RION, Tokyo, Japan). Stimuli consisted of two pure tones ( $f_1$  and  $f_2$ ,  $f_2/f_1=1.22$ ) presented simultaneously with the lower frequency stimulus at 65 dB and the higher frequency at 55 dB SPL. The total duration of measurements per ear was 3 min. During measurements, noise floors were  $-10\pm 5$  dB. DPOAEs were considered present when the signal-to-noise ratio (SNR) at each measured frequency was at least 3 dB.<sup>11</sup>

Statistical analyses were conducted using the Statistical Package for the Social Sciences 25.0 (SPSS) version for Windows. Descriptive statistics are expressed as means and standard deviation, and DPOAE amplitudes were compared between male and female patients. The statistical analysis was performed with 41 composite values of each group, using two independent samples t-test and the Mann-Whitney U test. Results with p values < 0.05 were considered significant.

All study protocols were approved by the ethics review committee of Nagoya Central Hospital, Nagoya, Japan

## RESULTS

### *Patients*

A total of 82 ears from 41 patients (21 men ranging from 11 to 54 years old, and 20 women ranging from 23 to 69 years old) were included. The mean age of the female patients was higher (47.8 years) than of the male patients (31.3 years).

*Otological symptoms*

Table 1 shows the subjects' otological symptoms, which included complaints of tinnitus, vertigo, and dizziness. Ten of the 21 male (47.6%) and eight of the 20 female (40.0%) patients had otological symptoms. The incidence of otological symptoms was similar in male and female patients. The incidence of tinnitus was higher than that of any other otological symptom.

**Table 1** Otological symptoms of the patients with Fabry disease

	Male	Female	Total
<b>Otological symptoms</b>	10	8	18
Tinnitus	5	5	10
Vertigo or dizziness	2	3	5
Tinnitus and vertigo or dizziness	3	0	3

*Other complications*

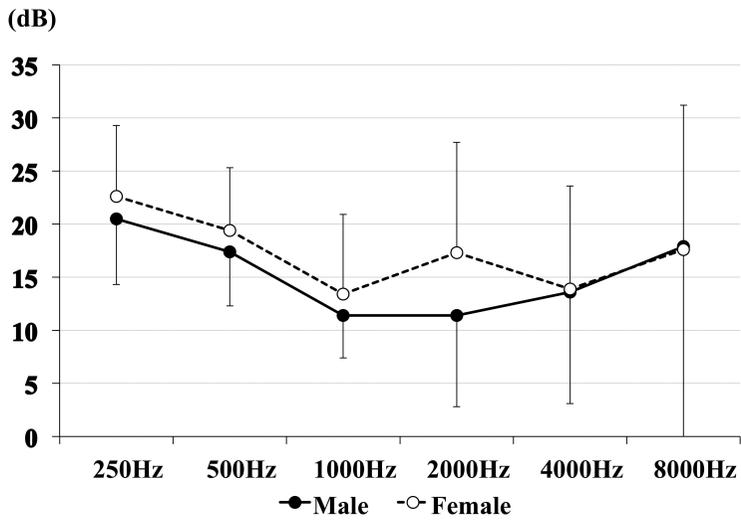
Table 2 shows other complications related to FD. Kidney function was evaluated by measuring serum creatinine (SCr), which was classified as dysfunctional at >0.8 mg/dL, and cardiac function was evaluated by brain natriuretic peptide (BNP), which was classified as dysfunctional at >19.5 pg/mL. Eight of 21 male patients had complications, and five of them had only cardiac dysfunction. Three of 21 male patients had kidney dysfunction, and two of them had cardiac dysfunction. Fourteen of 20 female patients had cardiac dysfunction, but there were no other dysfunctions. The incidence of cardiac dysfunction was higher in female than in male patients.

**Table 2** Other complications related to Fabry disease

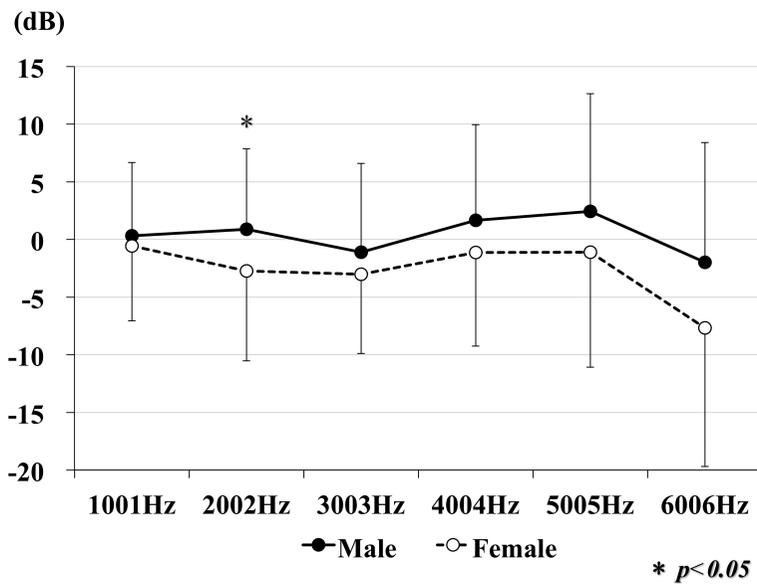
	Male	Female	Total
<b>Complications</b>	8	14	22
Cardiac dysfunction	5	14	19
Kidney dysfunction	1	0	1
Cardiac and kidney dysfunction	2	0	2

*PTA and DPOAE amplitude values (DP-gram)*

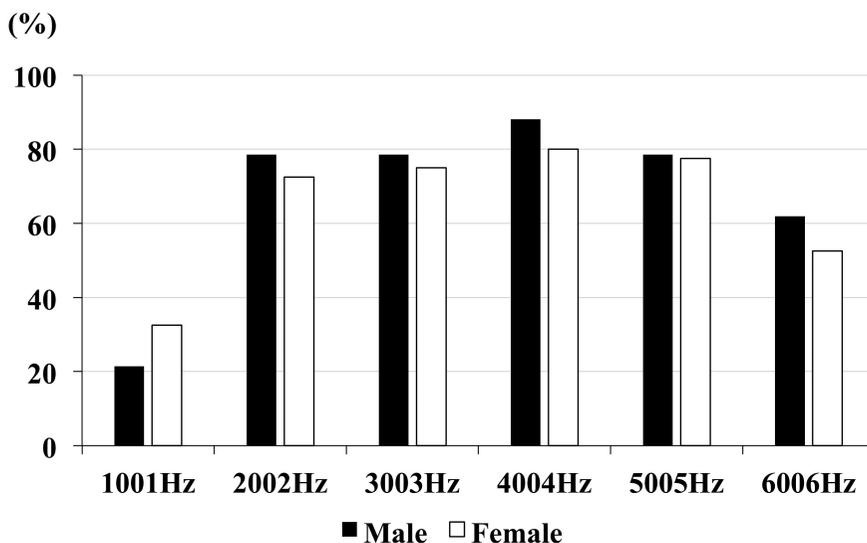
The paired data from left and right ears were combined into composite values using the average PTA and DPOAE amplitude values, resulting in 21 composite values for male patients and 20 composite values for female patients. Figure 1 shows the average and air-conduction hearing thresholds at six frequencies in male and female patients. The average thresholds of all frequencies were below 25 dB in male and female patients. Figure 2 shows the average and standard deviation of the DPOAE amplitude values at six frequencies. Both male and female patients had decreased DPOAE amplitudes at higher frequencies. At 2002 Hz, there were significant differences ( $P < 0.05$ ) between male and female patients.



**Fig. 1** The mean thresholds at six frequencies in male and female patients  
The average thresholds of all frequencies were below 25 dB in male and female patients.



**Fig. 2** The mean distortion product otoacoustic emission (DPOAE) amplitudes and standard deviations at six frequencies in male and female patients  
Both male and female patients had decreased DPOAE amplitudes at higher frequencies, and there were significant differences between male and female patients at 2002 Hz ( $P < 0.05$ ).



**Fig. 3** The rate of distortion product otoacoustic emission (DPOAE) responses at six frequencies in male and female patients

The DPOAE was low at frequencies of 1001 Hz and 6006 Hz in both male and female patients, and the rate was higher in male than female patients at all frequencies except for 1001 Hz.

#### *Presence of DPOAE*

Figure 3 shows the rate of DPOAE at all tested frequencies according to the SNR. The rate of DPOAE was low at frequencies of 1001 Hz and 6006 Hz in both male and female patients, and the rate was higher in male than in female patients at all frequencies except for 1001 Hz.

## DISCUSSION

Hearing loss is a well-known feature of FD, and other otological symptoms, including tinnitus, fullness, vertigo, and dizziness, have been reported. Sakurai et al reported that 66.7% of male and 33.3% of female FD patients with normal hearing had tinnitus.<sup>12</sup> The present study also showed a high incidence of otological symptoms in FD patients with normal hearing, with tinnitus being the most frequent. Tinnitus and vertigo or dizziness might suggest cochlear or vestibular disturbances, which would suggest different mechanisms of damage of the cochlea and vestibule.<sup>7</sup>

A recent study reported that renal and cardiac impairments could influence the severity of hearing loss,<sup>13</sup> and another study showed that hearing loss was strongly correlated with renal impairment.<sup>14</sup> Lysosomal storage could trigger a similar mechanism with the epithelial cells of the kidney and the outer hair cells representing a key target site of pathology.<sup>15</sup> In the present study, kidney dysfunction was observed in three male patients with normal hearing. Cardiac dysfunction was observed in male patients, but its incidence was high in female patients. Hearing loss and left ventricular hypertrophy could involve different pathological mechanisms.<sup>14</sup>

DPOAEs could be used to monitor the progression of cochlear disturbances during the early stages of hearing impairment. When DPOAEs are present and normal in amplitude and configuration, their presence indicates that the cochlear amplifier is functioning normally.<sup>11</sup> In the present study, DPOAE amplitude was decreased in both male and female patients, although thresholds on PTA were in the normal ranges. The DP-grams may be predictive of a substantial

threshold shift for a given frequency before a measurable sensitivity loss.<sup>16</sup> In the present study, DPOAE amplitude was significantly different at frequencies of 2002 Hz between male and female patients, and the SNRs were lower at 1001 Hz and 6006 Hz. These data suggest that cochlear dysfunction may have occurred early, before hearing deterioration detected on PTA. The exact pathophysiological mechanism of the cochlear involvement deserves further studies.

The limitation of the present study was the small number of patients included, which could have led to selection bias because of the incidence of the otological symptoms and the comparison between male and female patients. In order to establish strong evidence, we are planning to increase the number of patients with FD for an age-sex matched comparison in the future. There were no data for DPOAEs in age-matched normal subjects. The mean age was higher in female than in male patients, which might influence the data for PTA and DPOAE, though the incidence of otological symptoms was similar between them.

Enzyme replacement therapy may provide some protection for the inner ear epithelium, which would be observed as stabilization of hearing loss.<sup>17</sup> DPOAE can detect the function of outer hair cells, indirectly reflecting cochlear functional status. Evaluation of DPOAE in patients with FD before and after enzyme replacement therapy might provide useful information regarding cochlear function.

## CONCLUSIONS

Patients with FD had a high incidence of otological symptoms, though their hearing levels were normal. In such patients, DPOAE might be a useful tool for monitoring cochlear disturbances.

## DISCLOSURE

No financial disclosure and no conflict of interest.

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