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Head-impulse testing in Fabry disease – vestibular function in male and female patients

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Aim: To study the prevalence of peripheral vestibular deficit in male and female patients with Fabry disease and to assess the effect of enzyme replacement therapy (ERT) on peripheral vestibular function using quantitative head-impulse testing. *Methods:* Using dual search-coils the vestibulo-ocular reflex during rapid rotational head thrusts to both sides was recorded in 21 patients (13 male, 8 female) with Fabry disease prior to ERT initiation. ERT consisted of infusions of gene-activated human α-galactosidase A (agalsidase alfa; Replagal™) every 2 weeks at doses of 0.2 mg/kg. Eight patients were tested again approximately 6 and 12 months after the initiation of ERT. *Results:* At baseline examination, 15 of the patients with Fabry disease (71%; 11 males, 4 females) showed reduced peripheral vestibular function. The deficit was unilateral in nine patients (3 females) and bilateral in six patients (1 female). The severity of the vestibular deficit was not significantly different between male and female patients. After 12 months of ERT, the average vestibular deficit on the weaker side tended to improve; however, the change was not significant ($p = 0.10$).

Conclusion: Fabry disease affects peripheral vestibular function in both male and female patients. Females seem to be affected less frequently than males, but, on average, vestibular deficits are not different between the two groups. To confirm or reject the tendency for vestibular improvement during ERT, more patients need to be tested and longer follow-up periods are required.

Key words: *Enzyme replacement therapy, Fabry disease, vestibular function, vestibular-ocular reflex*

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Fabry disease is an X-linked lysosomal storage disorder due to deficient activity of the enzyme α-galactosidase A (α-Gal A) (1). The resultant intracellular accumulation of globotriaosylceramide and related glycosphingolipids, particularly in the vascular endothelium, leads to renal, cardiac and cerebrovascular manifestations. In patients with very low enzyme activity, progressive glycosphingolipid accumulation leads to early death secondary to renal failure, stroke or myocardial infarction. Although Fabry disease predominantly affects males, females may also show manifestations of the disease due to random X-chromosome inactivation. Until recently, management has been symptomatic, consisting of non-specific treatments for cardiac, renal and cerebrovascular complications. Since enzyme replacement therapy (ERT) with human α-Gal A has been made available, several studies have shown clearance of storage material and even reversal of some of the signs of the disease (2, 3).

The main neurological manifestations in patients with Fabry disease consist of cerebrovascular abnormalities (ischaemic or haemorrhagic lesions), episodic painful crises (usually highlighting the clinical onset of disease), constant acroparaesthesias and symptoms arising from the involvement of structures innervated by the autonomic nervous system (4, 5). Some patients also report vertigo. To date, it is unclear to what extent vertigo in Fabry disease is indeed of vestibular origin; that is, whether presumed vestibular dysfunctions are localized along peripheral or central vestibular pathways. On the basis of diminished ocular responses upon caloric (reduced peak slow-phase eye velocity) and turntable (reduced gain and time constant of nystagmus) testing, Morgan et al. (6) suggested that, at least in part, the vertigo in patients with Fabry disease is due to peripheral vestibular involvement. Both caloric and turntable testing, however, have their limitations. While caloric testing provides only a non-physiological stimulation of the peripheral vestibular organ and may not be sufficient to identify a chronic peripheral vestibular lesion (7), turntable testing cannot quantify the function of both labyrinths separately.

The function of individual semicircular canals and their afferents can best be tested by the so-called head-

impulse test (8, 9). Search-coil recording allows a quantitative assessment of the ocular response during head movements in the planes of individual semicircular canals (10). Using the search-coil head-impulse test, we studied the prevalence of peripheral vestibular deficits in male and female patients with Fabry disease, as well as the effects of ERT on vestibular function.

Materials and methods

Subjects

Twenty-one patients (13 male, 8 female; aged 22–71 years) who had been diagnosed with Fabry disease were included in the study. All patients were tested during a baseline examination before receiving ERT. Eight of the patients (5 male, 3 female; aged 22–54 years) were also assessed regularly during treatment. ERT consisted of infusions of gene-activated human α-Gal A (agalsidase alfa; Replagal™; TKT Europe – 5S, Danderyd, Sweden) every 2 weeks at a dose of 0.2 mg/kg (time range of treatment, 0–19 months). The comparison group consisted of 11 healthy subjects (6 men and 5 women; aged 25–59 years).

Informed consent was obtained from patients and control subjects after a full explanation of the experimental procedure. The protocol was approved by a local ethics committee and was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki for research involving human subjects.

Quantitative head-impulse testing

Eye and head movements were recorded in a magnetic frame (Remmel type system, modified by A. Lasker, Baltimore, MA, USA) using dual search-coils (Skalar Instruments, Delft, The Netherlands), which were calibrated before each session (see Straumann et al. (11) for details). After anaesthetizing the conjunctiva with oxybuprocaine 0.4%, one search-coil was placed on the right eye around the cornea and the other was tightly fixed on the forehead with adhesive tape. Voltages were sampled at 16 bits at a frequency of 1000 Hz and stored on the hard disk of a computer.

During experiments, subjects were seated inside the magnetic coil frame (side length: 1.4 m). Care was taken to position the centre of the interpupillary line in the centre of the magnetic frame. Horizontal head impulses (amplitude, 20–40°; duration, 150–200 ms; peak velocity, $\sim300°/s$; peak acceleration, $\sim10000°/s^2$) were applied by the investigator standing behind the subject. The directions of head impulses were pseudorandomly intermingled; four to six head rotations were applied to each side. Subjects were instructed to always fixate straight ahead on a light dot 1.24 m away.

Data analysis

Digitized signals were processed using interactive programs written in MATLAB® Version 6.5. The gain of the vestibulo-ocular reflex, g, was computed by:

$$g = 1 - \frac{\Delta e_s[h_0; h_1]}{h_1 - h_0}$$

where h_0 and h_1 are head-in-space positions, and Δe_s the difference between eye-in-space positions at $h_0 = 3°$ and $h_1 = 7°$. Traces of head impulses traversing the position interval $[h_0; h_1]$ were relatively straight. Median gains during head impulses to the right (G_R) and left (G_L) side were calculated.

Results

Typical eye and head traces during horizontal head impulses to both sides in a healthy subject and a patient with Fabry disease at baseline examination are shown in Fig. 1. In the healthy subject, gains were symmetrical, but not completely compensatory. In the patient with Fabry disease, gains were asymmetrical. In this example, the gain was reduced for head impulses towards the left. Overall, 15 patients with Fabry disease (71%) showed reduced gains. In six males and three females, gains for head impulses towards one side (left or right) were reduced, corresponding to a unilateral vestibular deficit. Gains in the remaining six patients, one of whom was female, were diminished towards both sides, equivalent to a bilateral peripheral vestibular deficit.

Average gains during head impulses towards the stronger and weaker side in male ($n = 13$) and female ($n = 8$) patients at baseline examination are plotted in Fig. 2. For head impulses towards the weaker side, the average gain in male patients was 0.59, which is reduced compared with healthy subjects. On the other hand, the average gain for head impulses towards the stronger side was 0.79, which is within the normal range. The difference in average gains between the two sides was significant (paired t-test: $p < 0.0001$). For female patients, the average gain on the weaker side was 0.68, which is almost normal, and towards the stronger side it was approximately 0.84. The difference in average gains between the two sides was significant (paired t-test: $p < 0.01$). There was no significant difference in gain between the male and female patients, comparing the stronger and weaker sides separately (unpaired t-tests: $p > 0.05$).

Gains before and during ERT are depicted in Fig. 3. Patients ($n = 8$) were tested at approximately 6 and 12 months after the initiation of therapy. For both male and female patients, no significant changes in average gain were noted after 12 months of ERT (paired t-test: $p = 0.10$). For the weaker side, gains transiently decreased within the first 6 months; however, there was a tendency for the gain to be higher than baseline after 12 months of treatment.
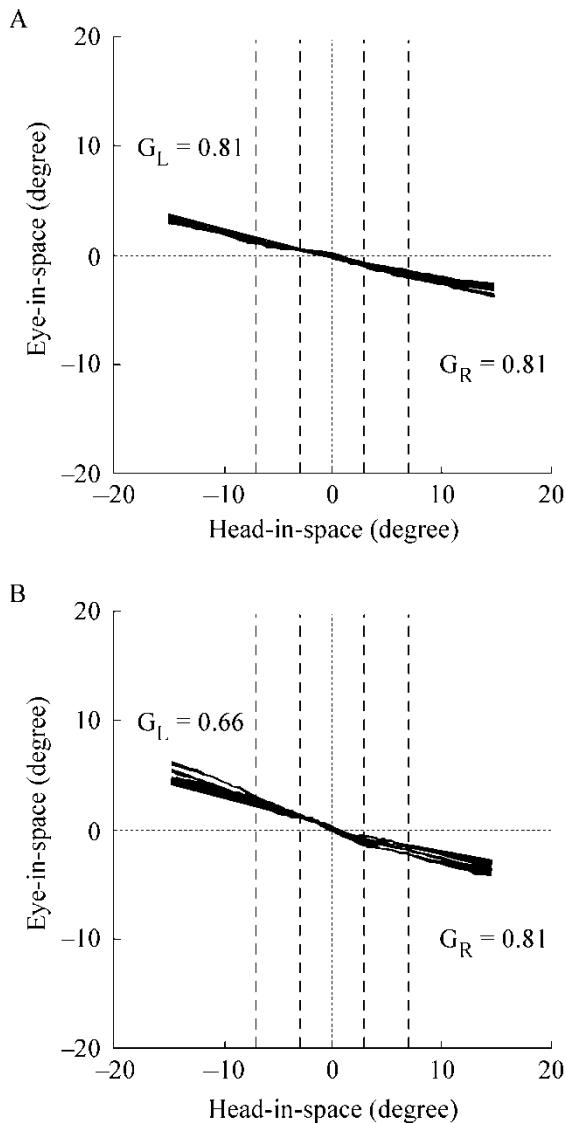
A

B

Fig. 1. Examples of horizontal head impulses in (A) a healthy subject, and (B) a patient with Fabry disease at baseline examination. If the vestibulo-ocular reflex were perfectly compensatory, traces would be parallel to the abscissa (head-in-space axis); if the vestibulo-ocular reflex were absent, traces would move on a 45° slope. G_R: median gain value for head impulses to the right; G_L: median gain value for head impulses to the left. Traces are clipped beyond 15° eccentricity of head-in-space. Dashed vertical lines indicate intervals used to determine the gains (see Methods).

Fig. 2. Average gain values (error bars: ± 1 SD) during head impulses towards the stronger and weaker side in male ($n = 13$) and female ($n = 8$) patients at baseline. The shaded area corresponds to the average gain values of healthy subjects ± 2 SD.

Discussion

Previous studies have demonstrated deficits of the vestibulo-ocular reflex in the low and medium frequency range in patients with Fabry disease using caloric irrigation and turntable testing (6). Applying the search-coil head-impulse test, we found that the vestibulo-ocular reflex of patients with Fabry disease is deficient during high-acceleration head rotations.
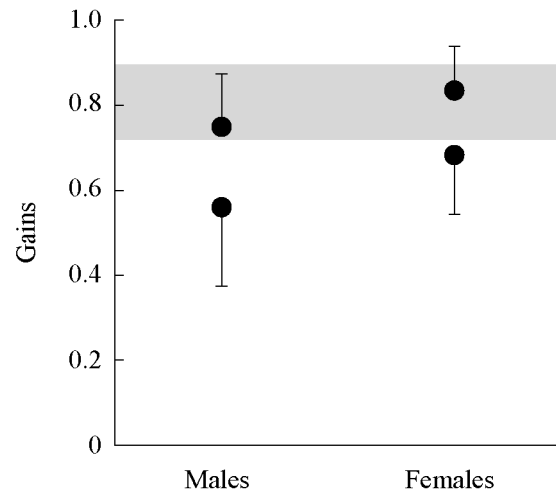
Such vestibulo-ocular reflex hypofunction in response to high acceleration is highly suggestive of a peripheral vestibular deficit; that is, lesions within the vestibular labyrinth or along the primary vestibular neuron (7, 9, 10). Thus, it is plausible that decreased peripheral vestibular function accounts, at least in part, for the vertigo that patients with Fabry disease occasionally report. This finding, of course, does not preclude other causes of vertigo, for example, lesions along the central vestibular pathways as a result of abnormal cerebrovascular circulation (12, 13).

We can only speculate on the pathogenesis of the peripheral vestibular deficit in patients with Fabry disease, as measured ocular responses during head impulses do not allow us to distinguish between labyrinthine or vestibular nerve lesions. The auditory dysfunction of patients with Fabry disease suggests damage at the level of hair cells (6). Assuming a similar pathogenesis for the vestibular system, one may also find that hair cells in the ampullae of the semicircular canals are damaged. Alternatively, lipid deposition along vestibular neurons could impair electrical signal conduction. Such lipid depositions, however, are more prominent in the autonomic nervous system of patients with Fabry disease (14, 15). A further possibility is that endothelial glycosphingolipid deposition in vestibular arteries could lead to ischaemic lesions of both the labyrinth and the vestibular nerve.

Surprisingly, impairment to the peripheral vestibular system in patients with Fabry disease was not symmetrical. This finding may indicate that endothelial pathogenesis dominates, as asymmetry of ischaemic lesions is a regular finding in vascular diseases. Morphological studies will be needed to determine the
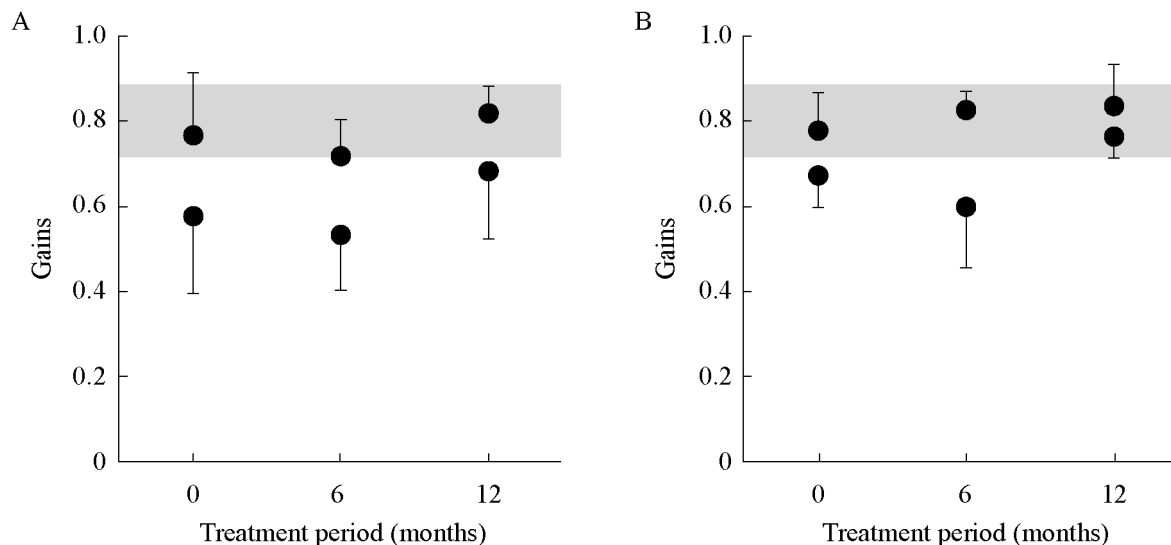
Fig. 3. Average gain values (error bars: ± 1 SD) for head impulses towards the stronger and weaker side in (A) male and (B) female patients at baseline and during enzyme replacement therapy.

exact causes of the peripheral vestibular deficit in patients with Fabry disease.

Previously, it has been suggested that females with Fabry disease also show signs of peripheral vestibular impairment, but so far the evidence has been limited (6). Our study provides clear evidence for peripheral vestibular deficits in female patients. As in male patients, peripheral vestibular deficits in female patients were mostly asymmetric. Although the severity of the clinical manifestations of Fabry disease in females is generally more variable than in males, ranging from asymptomatic to as severe as that in affected males, we found no significant difference in the severity of peripheral vestibular deficits between male and female patients.

Several studies have shown reversal of disease-related abnormalities in patients with Fabry disease given ERT (2, 16, 17). In our study, a subset of patients was tested before and 6 and 12 months after the initiation of ERT. In both male and female patients, there was a tendency for the weaker side to improve after 12 months of treatment. This improvement, however, was not significant. Possibly, with an increased number of patients, we may be able to demonstrate a significant improvement in vestibular function. However, as restoration of vestibular function, such as repair of nerves or hair cells, may be delayed relative to the clearing of the glycosphingolipid deposits, a longer follow-up period is also required.

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