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RESEARCH ARTICLE

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The vestibular and oculomotor dysfunction in Fabry disease: a cohort study in China

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ABSTRACT

Objective: Whereas a few studies have evaluated vestibular involvement in Fabry disease (FD), the relationship between vestibular/oculomotor abnormalities and disease-specific biomarkers remain unclear. Therefore, we seek to evaluate these quantitatively and analyze their relationship with disease phenotype and biomarkers in FD.

Methods: This cohort study enrolled 37 Chinese FD patients registered in our center. The vestibular/oculomotor examinations were performed, including the videonystagmography, the caloric test and the video head-impulse test. Statistical analyses were made between different subgroups of patients.

Results: Visuo-oculomotor dysfunctions were found in 30/37 (81.1%) patients. Vestibulo-oculomotor dysfunctions were revealed in 9/22 (40.9%) patients. Statistical tests showed: (1) significantly higher Mainz Severity Score Index in patients with prolonged saccade latency [20(18,33) VS 13(9,22), $p=0.008$] and vestibulo-oculomotor dysfunction [23(20,31) VS 9(5.5,12.5), $p=0.024$], (2) significantly higher total small-vessel disease score in subgroups with prolonged saccade latency [2.5(1,3.5) VS 1(0,2), $p=0.038$], defective smooth pursuit [3(2,4) VS 1(0,2), $p=0.003$], defective optokinetic nystagmus [4(2,4) VS 1(0.2), $p=0.009$] and vestibulo-oculomotor dysfunction [1(1,3) VS 0(0,1), $p=0.028$], (3) significantly lower α-Gal A activity (μmol/L/h) in subgroups with defective saccades [0.44(0.25,1.93) VS 1.85(0.75,5.52), $p=0.015$] and defective smooth pursuit [0.30(0.17,0.44) VS 0.96(0.39,2.40), $p=0.008$], and (4) significantly elevated plasma globotriaosylsphingosine (ng/ml) in patients with defective saccades [74.16(11.05,89.18) VS 10.64(7.08,36.32), $p=0.034$], than in patients without those abnormalities.

Conclusion: A high incidence of extensive vestibular and oculomotor dysfunction was observed in patients with FD, with the neuro-otological dysfunction being closely related to the disease burden and biomarkers like α-Gal A activity and lyso-Gb3.

KEY MESSAGES

The extensive vestibular and oculomotor dysfunction in FD patients were closely related to the disease burden and biomarkers like α-Gal A activity and lyso-Gb3.

When vestibular dysfunction is identified in FD patients, a multi-system evaluation should be conducted to early discover the damage of important organs.

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1. Introduction

Fabry disease (FD, OMIM301500) is a rare X-linked lysosomal storage disease caused by GLA gene mutation, which decreases the activity of α-galactosidase A (α-Gal A), then increases the storage of enzymatic substrates as globotriaosylceramide (Gb3) [1]. Gb3 deposits in many types of parenchymal cells, leading to the dysfunction of multiple organs including the heart, kidney, brain, skin, eyes, and gastrointestinal tract [2]. The broad range of multi-organ and multi-system involvements in FD do not spare the cochleovestibular system. Otologic histopathology showed glycosphingolipid accumulation in vascular endothelial and ganglion cells, as well as atrophy of the stria and spiral ligament, which might explain the otoneurologic symptoms like hearing loss and vestibular dysfunctions in patients with FD [3, 4].

High incidence of auditory symptoms has been reported in patients with FD, with the frequency of

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hearing loss being higher in men than in women [3, 5, 6]. However, previous studies generally suggested that vestibular deficits in FD patients are less frequent [7, 8], and studies focusing on comprehensive vestibular evaluation were rare [9]. The potential correlations between vestibular/oculomotor abnormalities and brain lesions, disease burden, as well as the disease specific biomarkers such as α-Gal A and Lyso-Gb3 in FD, remain unclear. There is no exact data on the incidence of FD in the Chinese population, though an incidence rate of 0.12% in end-stage renal failure patients with dialysis has been reported [10]. Several studies from different centers revealed definite renal impairment [11], hypertrophic cardiomyopathy [12], and ocular involvement [13] in Chinese patients, with the incidence rate of hearing loss reported to be 37.5% in males [14], yet the vestibular dysfunction has not been noted.

In our previous work, intermittent and fluctuating dizziness were observed in approximately half of the FD patients, and 65.9% of them presented with abnormal brain MRI, indicating probable association between their vestibular dysfunction and cerebral small vessel pathology [15]. Therefore, the aims of this study are two folds: 1) to summarize the vestibular and oculomotor abnormalities characteristic of FD, and 2) to identify the potential factors influencing the vestibular and oculomotor function by evaluating the relationship between those abnormalities and the clinical aspects and biomarkers.

2. Materials and methods

2.1. Patient data and subgroups

This cohort study enrolled 37 patients with FD, with an age range of 13 to 64 years, selected from 236 FD patients who visited Peking University First Hospital from January 2001 to September 2023 (Figure 1). Diagnostic criteria were based on the typical clinical symptoms, family history and laboratory results (including GLA gene, α-Gal A activity, and plasma Lyso-Gb3) according to Chinese consensus in 2021 [10]. The cohort included two parts: 1) the retrospective cohort, comprising 11 FD patients who underwent the vestibular examinations in our center for medical purpose from January 2001 to November 2021. Written informed consent for participation and publication were signed on their follow-up visit during the study period after December 2021. Patients who did not maintain follow-up after December 2021 or refused the consent were excluded. 2) the prospective cohort, comprising 26 FD patients who underwent regular follow-up from December 2021 to September 2023. Written informed consent for participation and publication was obtained from these patients or their guardians. Patients refused to participate in the study were excluded. We recruited 37 age and gender-matched normal controls from the Health Management Center of Peking University First Hospital during 2021 to 2023, which comprised individuals aged ± 3 years with written consent obtained. The

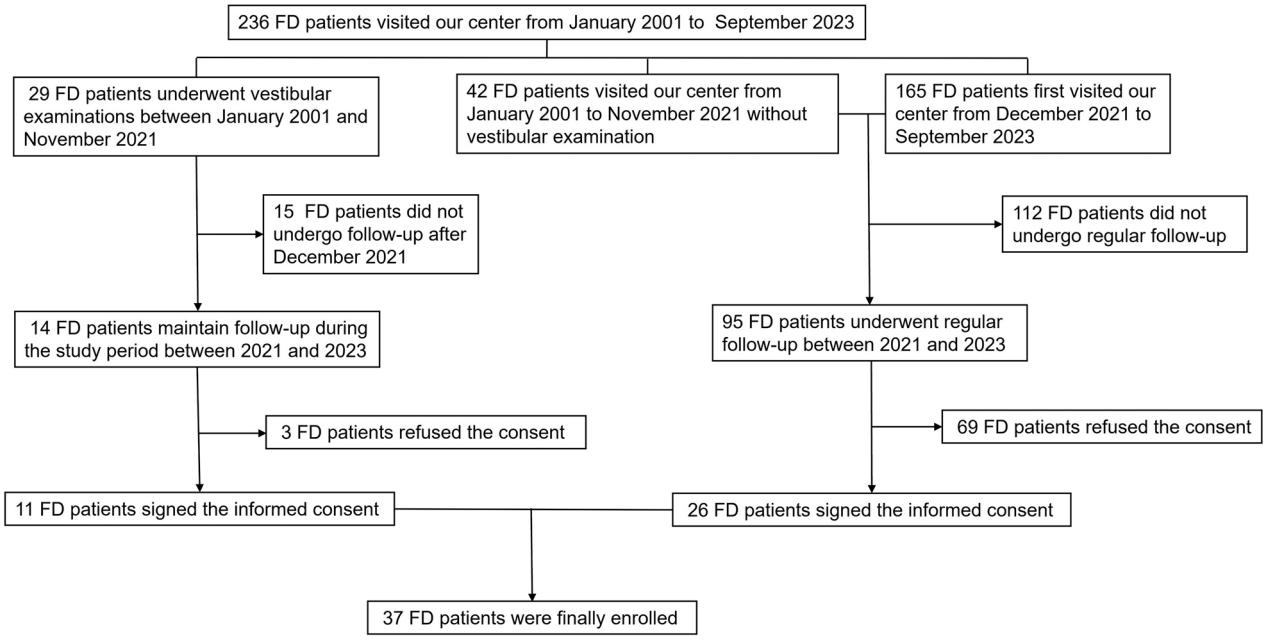

Figure 1. Flowchart of patient enrollment.

study was performed in accordance with the ethical standards of the relevant national and institutional committees on human experimentation. The study protocol strictly followed the guidelines of the Declaration of Helsinki (Version 2013).

Besides neuralgia, renal, cardiac and stroke events, we performed a thorough investigation of vestibular and auditory symptoms, including dizziness/vertigo, imbalance, tinnitus and hearing loss. Hearing impairment were identified by pure tone audiometry tests. The history of pathological neonatal jaundice, congenital deafness and other conditions causing auditory symptoms was excluded. Indicators of renal (eGFR) and cardiac involvement (left ventricular mass index, LVMI) were also recorded. MSSI was scored to evaluate global clinical status. Brain MRI data were obtained using 3 T scanners (3.0 T, GE 1.5 Sigma Twin Speed; GE Healthcare, Waukesha, WI, USA) with T1-weighted imaging, T2-weighted imaging, T2 fluid-attenuated inversion recovery, and diffusion-weighted imaging sequences. Cerebral small vessel disease burden was evaluated using total small-vessel disease score (SVDS) [16, 17].

According to their clinical symptoms, *GLA* mutations, α-Gal A activity and lyso-Gb3 [10, 18], 33 patients were classified as 'classic' disease type and 4 patients as 'non-classic' type. The criteria for a definite diagnosis of classic type were: (1) a variant in the GLA gene, (2) severely decreased or absent α-Gal A activity, usually <5% of the normal mean (for male patients only), and (3) a minimum of 1 of the following criteria: Fabry neuropathic pain, cornea verticillate, angiokeratoma, increased plasma lyso-Gb3, or (4) an affected family member with a definite diagnosis according to the criteria above. The other patients, with generally less severe symptoms, or disease manifestations limited to a single organ, or residual α-Gal A activity and lower level of lyso-Gb3 (for male patients), were classified as non-classic type. Mutations in the *GLA* gene were divided into truncated (frameshift or nonsense mutation) or non-truncated (missense or splicing mutation) mutation.

2.2. Vestibular examination

The visuo-oculomotor examination was conducted on 37 patients and 37 controls. The vestibulo-oculomotor examination was performed in 22 patients.

2.2.1. Visuo-oculomotor examination

The visuo-oculomotor examination included recording of gaze-evoked nystagmus (GEN) and oculomotor movements by a computer-based videonystagmography (VNG) system (Bao Runtong Research Ltd. China) [19, 20]. The participant was first asked to look forward in a dark room without any target and eye movements were recorded for 60s to identify spontaneous nystagmus and saccadic intrusions. Then several visuo-oculomotor tasks were performed as follows:

Gaze-holding test: The participant was asked to fix their gaze on a central target, and then on eccentric targets of ±15° horizontally, 10 s in each position. Nystagmus beating toward the direction of the target during the fixation was recorded as GEN.

Reflexive saccade test: The participant was instructed to fixate on the central spot (0°). The primary target extinguished simultaneously with the appearance of a peripheral target. Timing (1.0–1.5 s) and position of the target (2 times of ±5°, ±10°, ±15°, ±20°, ±25°, and ±30° horizontally) appeared randomly on the screen. The participant was instructed to visually track the target as rapidly as possible. The latency (the interval between target presentation and the start of the saccade), peak velocity, and accuracy/gain (saccade amplitude/target amplitude) of each saccade were measured by the computer. Abnormal saccades with prolonged latency (>250ms), slow peak velocity (below different reference value of each angle), hypometria (decreased gain <0.7), hypermetria (increased gain >1.15) and dysmetria (gain <0.7 or >1.15) were qualitatively recorded [21].

Smooth pursuit (SPM) test: The participant was required to visually pursuit a sinusoidally moving target smoothly. The target moved in the horizontal direction with an amplitude of ± 15° at a frequency of 0.2 Hz. The gain (eye velocity/target velocity) for the left and the right directions were calculated separately by computer. Defective SPM were defined as pursuit gain decreased below 0.6 or saccadic wave appeared upon sinusoidally trajectory (saccadic pursuit).

Optokinetic test: The participant was asked to visually track a series of targets continuously moving at a constant speed in the whole vision field as rapidly as possible, and the optokinetic nystagmus (OKN) was induced. The gain (the slow phase velocity of OKN/target velocity) was calculated by the computer, and defective OKN was judged with a gain < 0.6.

2.2.2. Vestibulo-oculomotor examination

The vestibulo-oculomotor examination included the caloric test and the video head-impulse test (vHIT).

Caloric test: 250 ml of 30 °C-cold and 44 °C-warm water was irrigated unilaterally into each ear during 30 s, then eye movement responses were recorded for 90 s by the VNG system. The slow phase velocity (SPV)

of the nystagmus induced by cold and warm water in each ear was calculated by the computer, recorded as LC, LW, RC and RW. The canal paresis (CP, or dissymmetry ratio) was calculated as follows:

$$CP = \frac{(RW + RC) - (LW + LC)}{RW + RC + LW + LC} \times 100\%$$

Unilateral weakness (UW) of the horizontal semicircular canal (SC) was defined as the summation of SPV in one ear (i.e. LC+LW, or RC+RW) <12°/s, or |CP|>30%.

Bilateral weakness (BW) was defined as both LC+LW and RC+RW <12°/s.

Video head-impulse test: Rotational head thrusts were applied approximately along the planes of the horizontal, left anterior and right posterior (LARP), and right anterior and left posterior (RALP) SCs by an investigator standing behind the subject. Three-dimensional eye and head movements were measured by the ICS impulse vestibular testing system (Natus Medical Incorporated). If the gain (eye velocity/head velocity) in any thrust direction was < 0.7 or compensatory saccades were recorded, the function of the SC in that direction was interpreted as abnormal.

2.3. Statistical analysis

IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA) was used for all analyses. Data with a normal distribution are given as the mean ± standard deviation, and data with a non-normal distribution are given as the median (range or interquartile range). Vestibular examination changes were compared between different clinical subgroups (males/females, classic/non-classic groups, different genotype groups and patient groups with/without specific clinical characteristics, i.e. vestibular symptoms, auditory symptoms, increased pure tone threshold and MRI changes). The age of examination, age of onset, disease duration, MSSI, SVDS, α-Gal A activities, and plasma Lyso-Gb3 levels were compared between subgroups with different vestibular examination changes (i.e. with/without visuo-oculomotor/vestibulo-oculomotor deficiency, slow saccades, prolonged saccadic latency, hypometria, hypermetria, defective saccades, defective SPM, and defective OKN). The independent samples t test and single factor ANOVA were used to analyze continuous variables with a normal distribution. The Wilcoxon rank-sum test was used to analyze continuous variables with a non-normal distribution and ordinal categorical variables. The Fisher's exact test was used to analyze unordered categorical variables. A p-value of <0.05 was considered significant.

3. Results

3.1. Clinical profiles

The 37 patients finally enrolled included 24 males and 13 females, from 31 unrelated families. The truncated *GLA* mutations were identified in 17 and non-truncated mutations in 20 of them. Twenty-eight patients (24 males and 4 females) showed decreased α-Gal A activity and 9 females had normal activity, and the median (interquartile range) value was 0.715(0.345, 2.145) μmol/L/h (Reference interval: >2.4 μmol/L/h). The plasma lyso-Gb3 were elevated in all patients and the median (interquartile range) value was 55.34 (6.92,84.74) ng/mL (Reference interval: <1.11 ng/mL).

Of the 37 patients, one (P34) was asymptomatic; the onset age of other 36 patients were 9(7,12) years old. The mean duration was 22.8 ± 2.5 years. Initial symptoms include neuralgia (26, 72.2%), proteinuria (4, 11.1%), arthralgia (2, 5.6%), sudden deafness (2, 5.6%), hypohidrosis (1, 2.8%) and palpitations (1, 2.8%). Five (13.5%) patients experienced stroke. Twenty-eight (75.7%) had auditory symptoms including tinnitus (18, 48.6%) and hearing loss (19, 51.4%), asymmetrical in 13 of them. Nineteen patients (51.4%) had vestibular symptoms including dizziness or vertigo, and 9 (24.3%) had balance disorders. The median onset age of these symptoms was 16. The median MSSI score was 18(9, 24) at the time of vestibular/oculomotor evaluation.

Complete audiometric data were available in 18 cases. Four (22.2%) cases were completely normal. Four (22.2%) patients presented with symmetrical bilateral hearing loss, including 2 with bilateral high-frequency sensorineural hearing loss (SNHL), 1 with bilateral flat SNHL, and 1 with bilateral mixed hearing loss (MHL). Six (33.3%) cases presented with asymmetrical bilateral hearing loss, including 2 with MHL on one side and SNHL on the other side, 3 with flat SNHL on one side and high-frequency or low-frequency SNHL on the other side, and 1 with low-frequency SNHL on one side and high-frequency SNHL on the other side. Four (22.2%) cases had unilateral hearing loss, including 1 with flat SNHL on the right side, 1 with flat SNHL on the left side, and 2 with high-frequency SNHL on the left side.

Thirty-one patients underwent brain MRI, 22(71.0%) of whom showed abnormalities mainly suggesting cerebral small vessel disease (CSVD), such as subcortical ischemic white matter lesions (WML), lacunar infarcts and cerebral microbleeds. Eight patients (21.6%) showed CSVD characteristics in infratentorial lesions and the ranges (medians) of SVDS was 0–3 (1.00). The main clinical features are listed in supplementary Tables S1–S3.

3.2. Visuo-oculomotor examination characteristics

In the visuo-oculomotor examination of all the 37 patients and 37 controls (Table 1 and Figure 2), the proportions of spontaneous nystagmus, GEN, and saccadic intrusions between the two groups were not statistically significant. The SPV of spontaneous nystagmus ranged from 0.6 to 3.7°/s, consistent with physical nystagmus. In the reflexive saccade test, smooth pursuit test and optokinetic test, the patients exhibited significantly higher prevalence of abnormalities in multiple parameters than controls. In general, the rate of impaired visuo-oculomotor performance in the patients was significantly higher than that in the control group.

In the patient group, the onset age of the patients in the subgroup with visuo-oculomotor deficiency was significantly older than those with normal visuo-oculomotor performance. The other clinical aspects were not statistically different between the two subgroups (Table 2).

3.2.1. Reflexive saccade test

The incidence rate of slow saccades in male patients was significantly higher than in females ($p=0.006$).

Table 1. Comparisons of visuo-oculomotor performance between FD patients and control subjects.

	FD Patients ($n=37$)	Control Subjects ($n=37$)	p-Value
Age, y	36.5 ± 15.0	36.4 ± 14.9	0.975
Sex, male/female	22/15	22/15	
Spontaneous nystagmus	7(18.9%)	4(10.8%)	0.258
Gaze-invoked nystagmus	1(2.7%)	0(0.0%)	0.500
Reflexive saccade test			
Abnormality	27(73.0%)	14(37.8%)	*0.002**
Slow saccade	14(37.8%)	3(8.1%)	*0.002**
Increased latency	12(32.4%)	1(2.7%)	*0.001**
Hypometria	20(54.0%)	8(21.6%)	*0.004**
Hypermetria	15(40.5%)	7(18.9%)	*0.037**
Saccade dysmetria	24(64.9%)	11(29.7)	*0.002**
Hypometric saccades(%)	4.17(0.00, 8.33)	0.00(0.00, 0.00)	*0.003**
Hypermetric saccades(%)	0.00(0.00, 8.33)	0.00(0.00, 0.00)	*0.027**
Dysmetric saccades(%)	8.33(0.00, 16.67)	0.00(0.00, 8.33)	*0.002**
Saccadic intrusion	13(35.1%)	6(16.2%)	0.055
Smooth pursuit test			
Abnormality	8(21.6%)	3(8.1%)	0.095
Saccadic pursuit	8(21.6%)	2(5.4%)	*0.043**
Decreased velocity gain	5(13.5%)	1(2.7%)	0.100
Velocity gain toward left	0.77(0.62, 0.84)	0.81(0.75, 0.89)	*0.009**
Velocity gain toward right	0.82(0.68, 0.89)	0.84(0.75, 0.91)	0.236
Impaired optokinetic nystagmus	5(13.5%)	0(0.0%)	*0.027**
Visual oculomotor deficiency	30(81.1%)	17(45.9%)	*0.002**

(*$p<0.05$).

Compared with the patients with normal saccade velocity, patients with slow saccades had significantly longer disease duration ($p=0.048$), higher MSSI ($p=0.029$), lower α-Gal A activities ($p=0.032$), and higher plasma Lyso-Gb3 levels ($p=0.009$) (Table 3 and Figure 3).

The patients with prolonged saccade latency were significantly older than patients with normal latency (42.5 ± 3.6 VS 33.3 ± 3.4, $p=0.041$), and had significantly longer disease duration ($p=0.004$), higher MSSI ($p=0.008$) and higher SVDS ($p=0.038$) than the latter (Table 4 and Figure 3).

The patients with hypometria were significantly older than those without hypometria (41.2 ± 3.5 VS 31.3 ± 3.4, $p=0.025$), and their SVDS were significantly higher than that of the latter group ($p=0.039$). The patients with hypermetria had significantly lower α-Gal A activities ($p=0.039$) and higher plasma Lyso-Gb3 levels ($p=0.025$) than those without hypermetria (Table 5 and Figure 3).

In general, the proportion of impaired saccade test performance in male patients was significantly higher than in females ($p=0.033$). The patients with defective saccades had significantly lower α-Gal A activities ($p=0.014$) and higher plasma Lyso-Gb3 levels ($p=0.034$) than those with normal saccade. There were no significant differences in the rates of saccadic abnormalities between the other clinical subgroups (Table 6 and Figure 3).

3.2.2. Smooth pursuit test

The patients with defective SPM, especially saccadic pursuits, had older age of onset ($p=0.045$), lower α-Gal A activity ($p=0.008$), and higher SVDS ($p=0.003$) than those with normal pursuits. There were no statistically significant differences in the rates of impaired smooth pursuits between any clinical subgroups (Table 7 and Figure 3).

3.2.3. Optokinetic test

The disease duration in patients with defective OKN was significantly longer than in patients with normal OKN ($p=0.021$), and their SVDS was significantly higher than the latter ($p=0.009$). No significant differences in the rates of defective OKN was identified between any clinical subgroups (Table 8 and Figure 3).

3.3. Vestibulo-oculomotor examination characteristics

In the 22 patients who performed vestibulo-oculomotor examinations, 9 (40.9%) were abnormal (Table 2).

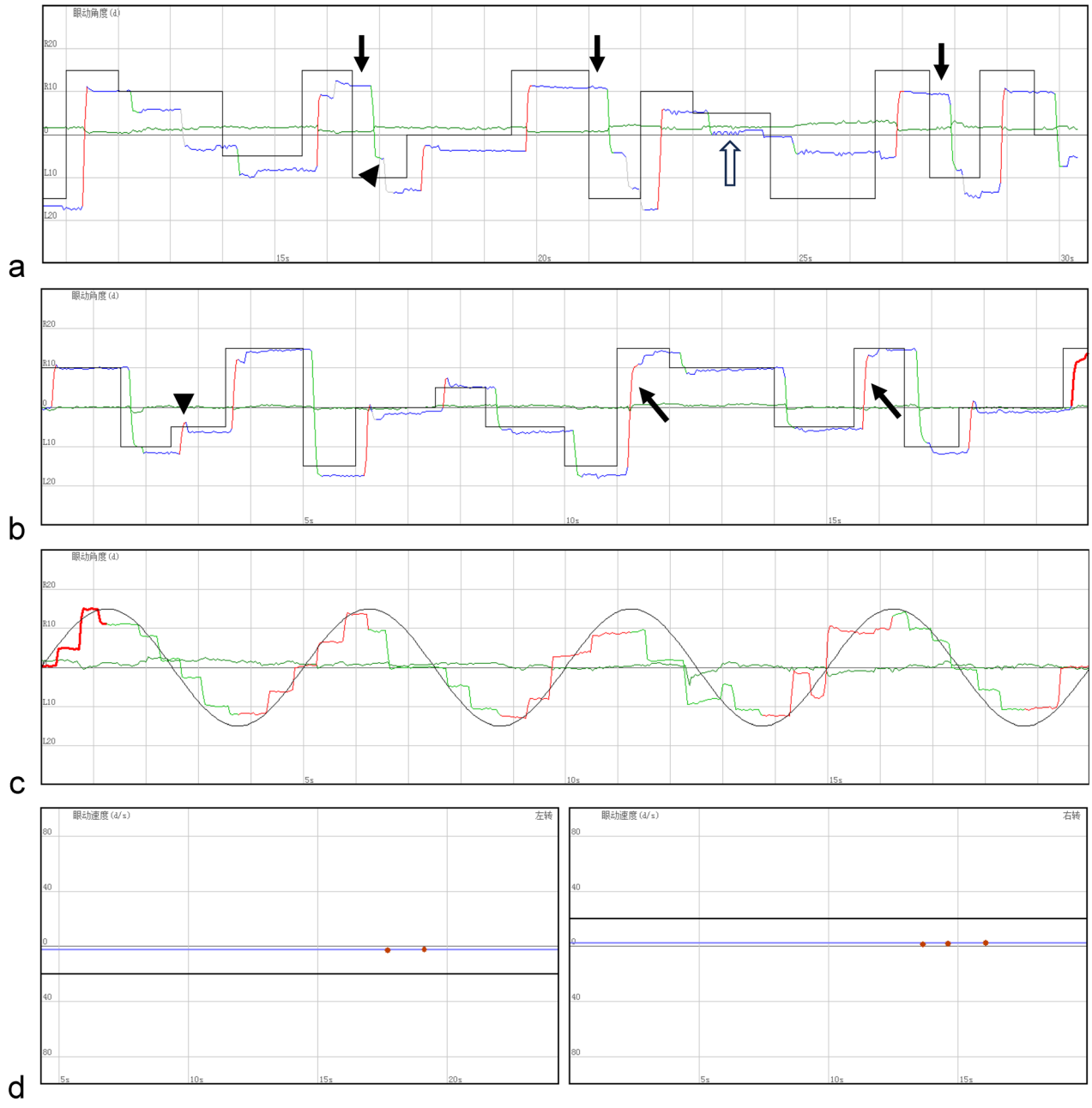

Figure 2. Visuo-oculomotor deficiencies in Fabry patients. A. Defective saccades of P20, showing increased latencies (black arrows), hypometria (arrow heads) and saccadic intrusions (hollow arrow); B. Defective saccades of P29, showing slow saccades (black arrows) and hypermetria (arrow heads); C. Defective smooth pursuits of P35, showing saccadic pursuits and reduced pursuit gain toward left (0.30) and right (0.33); D. Impaired optokinetic nystagmus of P35, showing reduced gain toward left (0.13) and right (0.10).

Bilateral impairments were revealed in 6 of them, and unilateral impairments in 3, involving one or more SCs (Figure 4a–d). Seven of them were complicated by symptomatic or subclinical hearing loss (ipsilateral or contralateral to the damaged SCs), or tinnitus (Figure 4e).

The disease duration in the patient group (Table 2 and Figure 5a–d) with impaired vestibulo-oculomotor performance was significantly longer than that in the patients with normal vestibulo-oculomotor function (32.0 ± 12.4 VS 17.9 ± 14.6, $p = 0.036$). The MSSI ($p = 0.024$) and SVDS ($p = 0.028$) in the vestibulo-oculomotor deficiency group were significantly higher than normal. The incidence rate of vestibulo-oculomotor deficiency in patients with symptomatic hearing loss was significantly higher than that in patients with normal hearing ($p = 0.040$). The other clinical subgroups showed no significant differences in the rates of vestibulo-oculomotor deficiency.

Besides the 9 patients with defective vestibulo-oculomotor performance, 1 patient who did not

Table 2. Correlations Between oculomotor performance and clinical characteristics of FD patients.

	Visuo-oculomotor tests			Vestibulo-oculomotor tests		
	Normal	Abnormal	p-value	Normal	Abnormal	p-value
Number	7	30		13	9	
Age, y	33.4 ± 14.0	37.3 ± 15.4	0.549	37.7 ± 17.4	40.2 ± 12.6	0.713
Gender, male/female	3/4	19/11	0.408	5/8	6/3	0.193
Disease duration, y	24.0 ± 14.8	21.6 ± 14.9	0.717	17.9 ± 14.6	32.0 ± 12.4	*0.036**
Age of onset, y	7(7,8)	9(7,15)	*0.008**	9(7,20)	8(7,9)	0.231
MR			0.577			0.066
Normal	2	7		5	1	
Abnormal	4	18		4	8	
Site of MR lesions			0.767			0.09
None	2	7		5	1	
Supratentorial only	3	11		3	6	
With infratentorial	1	7		1	2	
SVDS	1(0,1)	1(0.2)	0.091	0(0,1)	1(1,3)	*0.028**
Vestibular symptoms			0.532			0.305
None	3	15		7	3	
Vertigo, dizziness or imbalance	4	15		6	6	
Auditory symptoms			0.394			0.246
None	2	13		6	2	
Hearing loss or tinnitus	5	17		7	7	
Symptomatic hearing loss			0.468			*0.040**
None	4	14		9	2	
Symptomatic	3	16		4	7	
Pure tone threshold			0.468			0.119
Normal	1	4		3	1	
Impaired	1	13		1	5	
MSSI	13(9,24)	18(11,23)	0.215	9(5.5,12.5)	23(20,31)	*0.024**
Clinical type			0.585			0.642
Classic	6(18.6%)	27(81.8%)		11(57.9%)	8(42.1%)	
Non-classic	1(25.0%)	3(75.0%)		2(66.7%)	1(33.3%)	
Genotype			0.596			0.110
Truncated	3(17.6%)	14(82.4%)		4(40.0%)	6(60.0%)	
Non-truncated	4(20.0%)	16(80.0%)		9(75.0%)	3(25.0%)	
α-Gal A activity (μmol/L/h)	1.11(0.39,7.40)	0.60(0.30,1.95)	0.07	1.75(0.40,3.09)	0.72(0.48,1.58)	0.404
Plasma Lyso-Gb3 (ng/ml)	10.84(7.95,60.13)	67.94(10.43,88.31)	0.153	7.95(5.06,64.04)	68.06(30.13,100.82)	0.064

(*$p < 0.05$).

Table 3. Correlations Between slow saccades and clinical characteristics of FD patients.

	Slow saccades		
	With	Without	p-value
Number	12	25	
Age, y	34.4 ± 3.3	38.1 ± 3.6	0.506
Gender, male/female	11/1	11/14	*0.006**
Disease duration, y	26(22.5,31)	14.5(10,37)	*0.048**
Age of onset, y	9(7,10)	9(7,18)	0.204
MSSI	21(17,31)	13(9,23)	*0.029**
α-Gal A activity (μmol/L/h)	0.40(0.26,0.72)	1.43(0.35,2.40)	*0.032**
Plasma Lyso-Gb3 (ng/ml)	80.96(63.36,93.24)	11.78(6.20,81.23)	*0.009**
SVDS	2(0.5,3)	1(0,2)	0.163

(*$p < 0.05$).

undergo vestibulo-oculomotor tests rotated to one side of his body by an angle > 45° in Fukuda stepping test during clinical examination. Thus, the total number of patients with peripheral vestibular dysfunction was 10. The plasma Lyso-Gb3 in the peripheral vestibular dysfunction group were significantly higher than normal [80.79(40.00,97.80) VS 7.95(5.06,64.04), $p = 0.035$] (Figure 5e).

4. Discussion

There is a high incidence of auditory symptoms and not rare incidence of vestibular symptoms in our FD cohort, coincident with the previously studies reporting an incidence between 19 and 87% [7, 22–25]. Tinnitus may be the first auditory symptom, affecting approximately 27 ~ 38% of adult patients. Vestibular symptoms or subclinical vestibular deficits were identified in 25 ~ 80% of FD patients [3, 7, 8, 26]. Weak response in the caloric tests, indicating the peripheral vestibular deficits, was observed in the patients with severe systematic symptoms [27]. It is speculated that the mechanism of hearing impairment in FD patients is likely the damage to the cochlea itself, caused by Gb3 deposition in the stria vascularis and spiral ligament of the cochlea, rather than damage to the internal auditory artery (IAA) or auditory nerve [28]. Our data showed that the prevalence of peripheral vestibular dysfunction in patients with symptomatic hearing loss was significantly higher than that in patients with normal hearing, suggesting that the damage of vestibular organs often accompanies the damage of the cochlea, thus they may have a common pathological

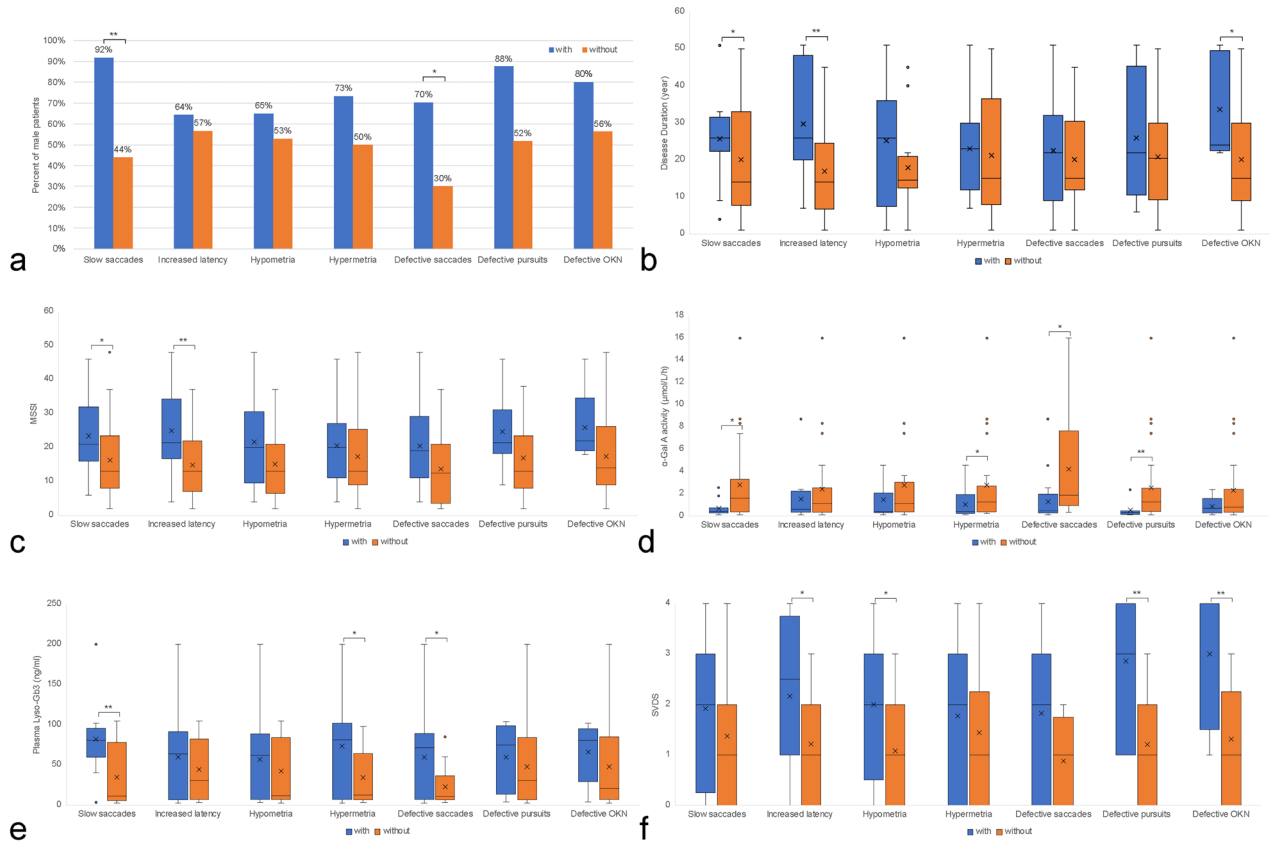

Figure 3. Clinical characteristics of the patients with/without certain visuo-oculomotor deficiencies. (*: $p < 0.05$; **: $p < 0.01$).

Table 4. Correlations Between prolonged saccade latency and clinical characteristics of FD patients.

	Prolonged latency		
	With	Without	p-value
Number	14	23	
Age, y	42.5 ± 3.6	33.3 ± 3.4	*0.041**
Gender,male/female	9/5	13/10	0.454
Disease duration, y	28(23,48)	14(7,22)	*0.004**
Age of onset, y	9(7,10)	9(7,12)	0.37
MSSI	20(18,33)	13(9,22)	*0.008**
α-Gal A activity (μmol/L/h)	0.60(0.40,2.07)	0.73(0.33,1.95)	0.413
Plasma Lyso-Gb3 (ng/ml)	71.38(11.05,89.18)	40.0(7.95,81.23)	0.287
SVDS	2.5(1,3.5)	1(0,2)	*0.038**

(*$p < 0.05$).

mechanism, which might be the degeneration caused by the deposition of Gb3 in the stria vascularis.

The characteristics of peripheral vestibular dysfunction in our study also support the above mechanism. Nearly half of the patients who underwent vHIT or caloric testing showed abnormalities suggesting peripheral vestibular dysfunction. It is important to note that peripheral vestibular damage in these patients is not consistent with the distribution area of vestibular nerve (VN) branches. The VN is divided into the superior and inferior vestibular nerves, the former innervating the anterior and horizontal SCs, and the latter the posterior SCs. In our patients, reduced vestibulo-ocular reflex gain or compensatory saccades in a single SC, or in SCs on different sides, were frequently present and could not be explained by dysfunction of the superior or inferior vestibular nerves. A few literatures have studied the vestibular function of FD patients. For example, Carmona et al. reported that 70% of vestibular and hearing impairment in FD patients could not be explained by lesions of a single blood vessel or nerve [29]. Consistent with this finding, our study also suggests that the peripheral vestibular dysfunction in Fabry patients is probably due to the lesions of the vestibular organ itself, rather than the damage of the IAA or VN.

In contrast to the vestibulo-oculomotor deficiency, the visuo-oculomotor deficiency in FD patients, which suggests the central vestibular dysfunction, was reported less frequently. Our patients had widespread visuo-oculomotor deficiency. Their deficits in saccades, SPM, and OKN were more common than in normal controls, indicating widespread impairment of the structures involving those eye movements. Those structures are mainly located in the brain stem and cerebellum (Figure 6). This feature is similar to CSVD and neurodegenerative diseases such as Parkinson's

Table 5. Correlations Between saccadic dysmetria and clinical characteristics of FD patients.

	Hypometria			Hypermetria		
	With	Without	p-value	With	Without	p-value
Number	20	17		15	22	
Age, y	41.2 ± 3.5	31.3 ± 3.4	*0.025**	36.2 ± 3.3	37.2 ± 3.8	0.855
Gender, male/female	13/7	9/8	0.341	11/4	11/11	0.14
Disease duration, y	28(9.5,35)	15(14,21)	0.088	23.5(14,30)	17.5(8,36.5)	0.216
Age of onset, y	9(7,11)	9(7.5,13.5)	0.397	9(7,10)	9(7,15)	0.484
MSSI	20(10,30)	13(10.5,20.5)	0.073	19.5(11,23)	13(9,26.5)	0.181
α-Gal A activity (μmol/L/h)	0.41(0.32,2.00)	0.80(0.36,2.18)	0.187	0.40(0.23,1.18)	0.96(0.38,2.22)	*0.039**
Plasma Lyso-Gb3 (ng/ml)	67.94(13.56,88.08)	12.51(9.19,82.98)	0.302	81.18(71.38,102.01)	16.38(7.08,64.04)	*0.025**
SVDS	2(1,3)	1(0,2)	*0.039**	2(0,3)	1(0,2)	0.298

(*$p < 0.05$).

Table 6. Correlations Between defective saccades and clinical characteristics of FD patients.

	Defective saccades		
	With	Without	p-value
Number	27	10	
Age, y	37.6 ± 3.0	34.2 ± 5.1	0.338
Gender, male/female	19/8	3/7	*0.033**
Disease duration, y	23.2 ± 3.0	21.4 ± 5.1	0.667
Age of onset, y	9(7,12)	8.5(7,13.5)	0.193
MSSI	19(11,29)	12.5(6.5,18.5)	0.059
α-Gal A activity (μmol/L/h)	0.44(0.25,1.93)	1.85(0.75,5.52)	*0.014**
Plasma Lyso-Gb3 (ng/ml)	74.16(11.05,89.18)	10.64(7.08,36.32)	*0.034**
SVDS	2(0.5,3)	1(0,1.5)	0.058

(*$p < 0.05$).

Table 7. Correlations Between defective SPM and clinical characteristics of FD patients.

	Defective SPM		
	With	Without	p-value
Number	8	29	
Age, y	41.4 ± 5.8	35.4 ± 2.9	0.31
Gender, male/female	7/1	15/14	0.075
Disease duration, y	21.8 ± 2.8	26.0 ± 6.2	0.387
Age of onset, y	11(9.5,21.0)	8(7,12)	*0.045**
MSSI	21.5(18.5,31)	13(9,23)	0.05
α-Gal A activity (μmol/L/h)	0.30(0.17,0.44)	0.96(0.39,2.40)	*0.008**
Plasma Lyso-Gb3 (ng/ml)	74.58(15.90,95.16)	47.67(6.87,84.74)	0.134
SVDS	3(2,4)	1(0,2)	*0.003**

(*$p < 0.05$).

Table 8. Correlations Between defective OKN and clinical characteristics of FD patients.

	Defective OKN		
	With	Without	p-value
Number	5	32	
Age, y	34(32,61)	37(21,47)	0.184
Gender, male/female	4/1	18/14	0.312
Disease duration, y	24(23,48)	20(10,30)	*0.021**
Age of onset, y	10(9,10)	9(7,12)	0.238
MSSI	22(20,23)	13(9,24)	0.065
α-Gal A activity (μmol/L/h)	0.70(0.41,0.73)	0.60(0.33,2.07)	0.326
Plasma Lyso-Gb3 (ng/ml)	80.79(55.34,88.31)	40.00(7.95,84.74)	0.238
SVDS	4(2,4)	1(0,2)	*0.009**

(*$p < 0.05$).

disease and Alzheimer's disease [30–33], but different from most focal cerebral infarctions, which usually result in apparent gaze palsy with abnormalities in only a few visuo-oculomotor items [34]. The incidence rates of spontaneous nystagmus, GEN, and saccadic intrusions in our patients were similar to that in normal controls, indicating that there might be no significant damage to the gaze stabilizing system. This also differs from focal infratentorial infarctions, in which marked spontaneous and gaze-evoked nystagmus is common [34, 35].

FD is often prone to affect the posterior circulation system, which may lead to ischemic dysfunction of its territory, mainly involving the brain stem and cerebellum [15]. However, according to our data, the patients with infratentorial lesions on MR do not seem to manifest central vestibular dysfunction more commonly. The similarities of their visuo-oculomotor abnormalities with CSVD and degenerative diseases suggest that other complex mechanisms might be involved besides infratentorial ischemic damage. On one hand, the patients might have small vessel lesions at some structures in the cerebral hemispheres (Figure 6), which also play a role in the visuo-oculomotor control [36]. On the other hand, autopsy and mouse models have confirmed the deposition of Lyso-Gb3 in the neurons of FD [37, 38], causing visuo-oculomotor abnormalities similar to those seen in some neurodegenerative diseases.

Certain visuo-oculomotor deficiencies appear to be related to the severity of the patients' condition. For example, saccade abnormalities, especially slow saccades, are more likely to be seen in male patients, and

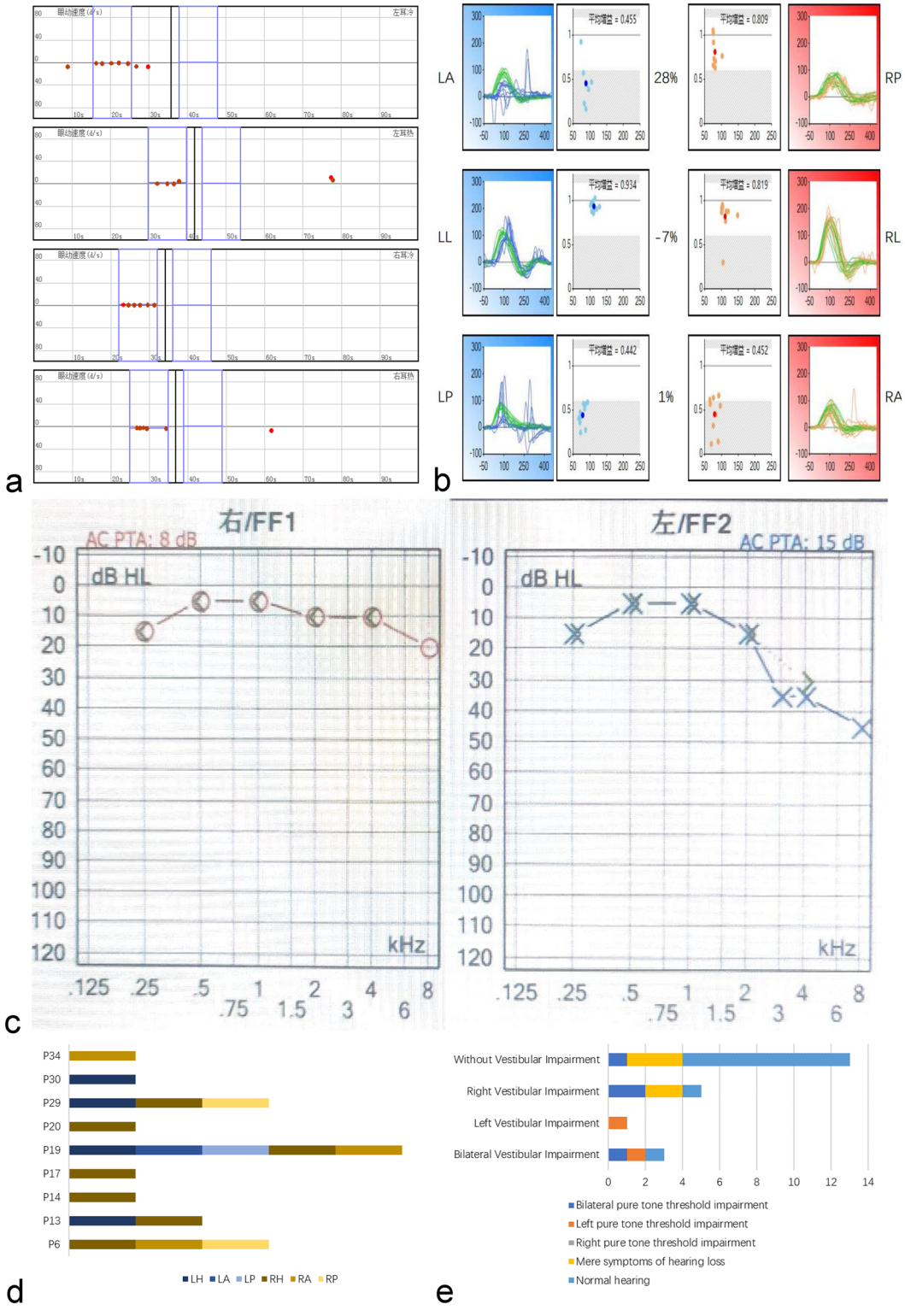

Figure 4. Vestibulo-oculomotor examinations and hearing loss in FD patients. A. Caloric test in P19, showing decreased SPV bilaterally (LC+LW = 2.5°/s, RC+RW = 3.3°/s), indicating bilateral weakness of horizontal semicircular canals; B. vHIT in P19, showing reduced gain in 3 semicircular canals bilaterally (LA, LP and RA), inconsistent with the distribution of a single nerve or vessel; C. Pure tone audiometry in P19, showing impaired threshold on the high frequency of the left side (35 dB HL on 4 kHz, 45 dB HL on 8 kHz). D. Dysfunction of semicircular canals in all the patients identified by caloric test and vHIT. E. Comorbidity of vestibular impairment and hearing loss in the patients.

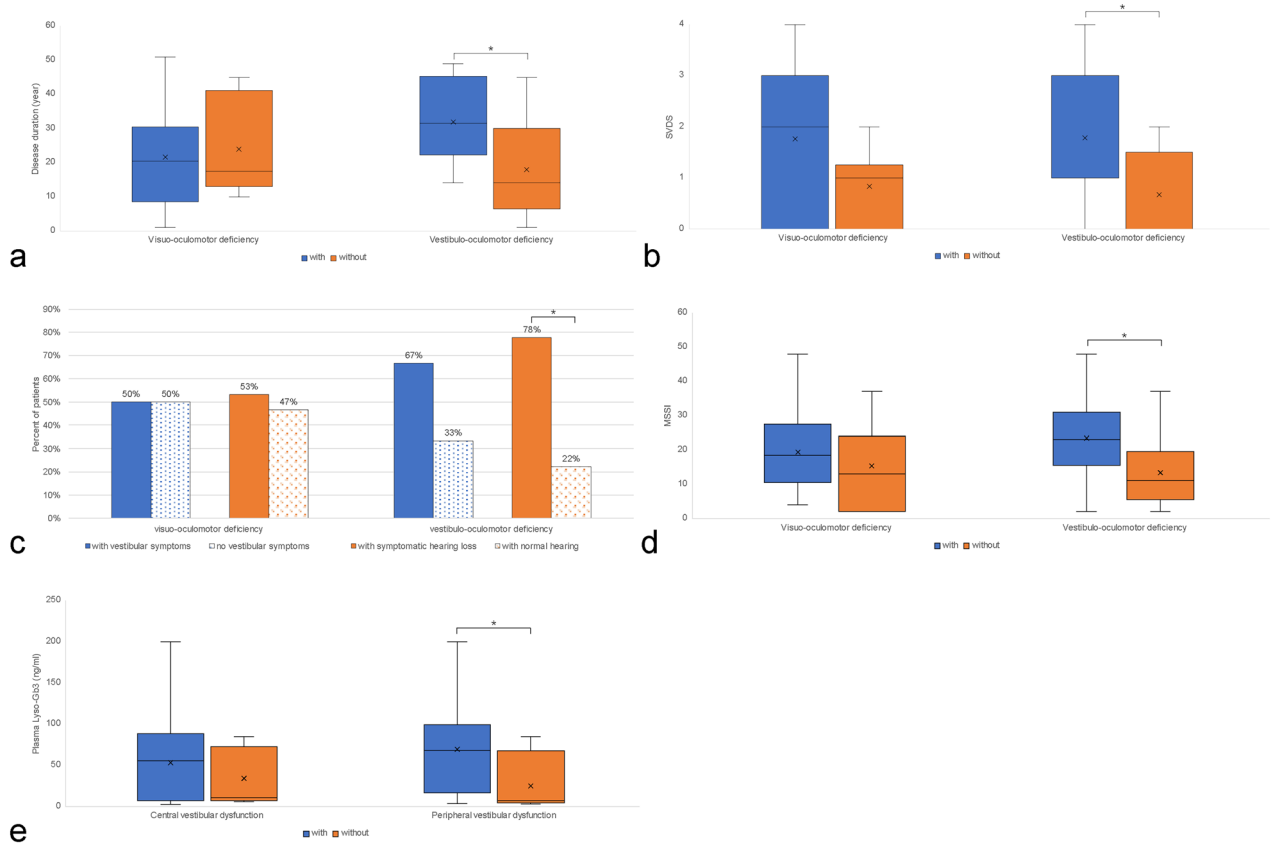

Figure 5. Clinical characteristics of the patients with/without visuo-oculomotor or vestibulo-oculomotor deficiencies. (*: $p < 0.05$; **: $p < 0.01$).

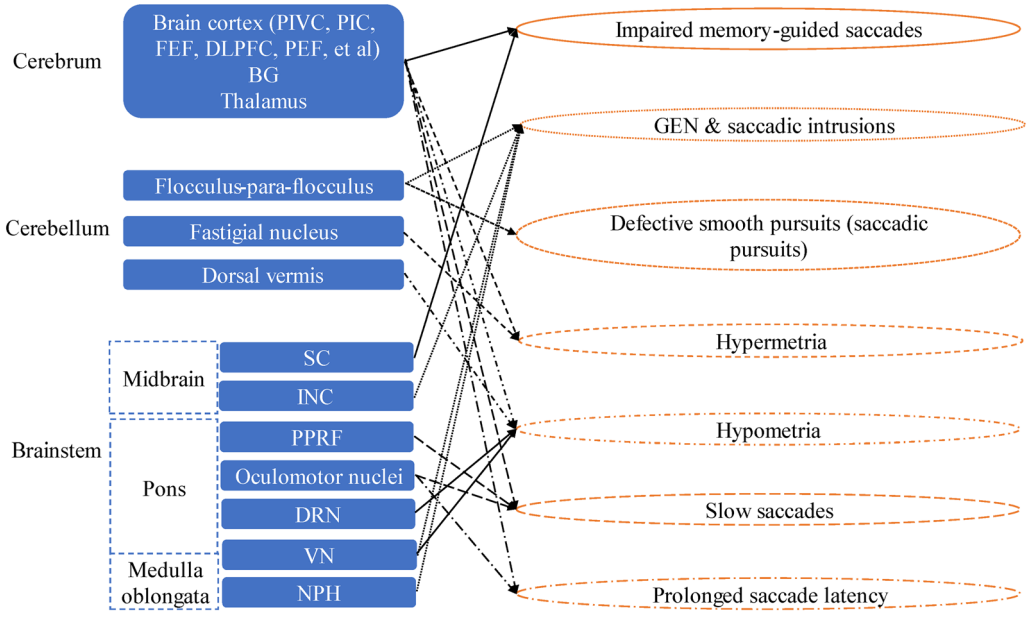

Figure 6. Schema of the brain structures related with visuo-oculomotor control (left row) and the manifestations of damage to them (right row). (PIVC, parieto-insular vestibular cortex; PIC, posterior insular cortex; FEF, frontal eye fields; DLPFC, dorsolateral prefrontal cortex; PEF, parietal eye fields; basal ganglia, BG; GEN, gaze-evoked nystagmus; SC, superior colliculus; INC, the interstitial nucleus of cajal; PPRF, paramedian pontine reticular formation; DRN, dorsal raphe nucleus; VN, the vestibular nuclei; NPH, the nucleus prepositus hypoglossi.).

these patients, together with the patients with hypermetria, have lower α-Gal A activity and higher plasma Lyso-Gb3 levels. Patients with prolonged saccade latencies have longer disease duration and higher MSSI. Patients with defective SPM also have lower α-Gal A activity. Although the rates of visuo-oculomotor deficiencies in the patients with/without MR lesions appear to be similar, the higher SVDS scores in those with prolonged saccade latency, hypometria, saccadic pursuits, and defective OKN might indicate a greater overall burden of CSVD. Similar damage of central vestibular system was also reported in Gaucher's disease [39] as biomarkers to monitor neurological deterioration. Therefore, the presence of extensive visuo-oculomotor abnormalities can also be used as a biomarker to predict or monitor the progression of FD.

Peripheral vestibular damage may also be a biomarker of FD progression according to the current study. Our data showed that patients with impaired peripheral vestibular function had longer disease duration, higher MSSI, and higher plasma Lyso-Gb3 levels, indicating a more severe overall disease burden. Interestingly, the SVDS in those patients were also higher, suggesting that peripheral vestibular damage and central small vessel disease seem to parallel. This corroborates the above speculation that the mechanism of peripheral vestibular damage in FD may be the deposition of substrates in the stria vascularis of the inner ear, similar to and simultaneous with the deposition in the endothelium of small vessels in the brain.

Although the above evidence supports the pathology of Gb3 deposition, the pathogenic pathway remains unclear. It is definitely known that the deposition of Gb3 in FD patients is followed by inflammatory activation [40]. The binding of Gb3 to toll-like receptor 4 can trigger Notch1 signaling and activate the nuclear factor kappa B signaling cascade, which results in the production of pro-inflammatory cytokines, leading to a chronic inflammatory state and associated vasculopathy [41]. The long-lasting inflammation results in fibrosis and tissue injury [42]. As a small anatomical structure, the inner ear could be vulnerable to inflammation. Recently we have identified a spectrum of inflammatory cytokines (ICs) which are upregulated in FD patients and positively correlate with disease burden, especially IL-8, which is higher in the high MSSI subgroup than in the low MSSI subgroup [40]. It can be speculated that the vestibular dysfunctions, which also showed some relevance with MSSI in this study, might be accompanied by the upregulation of those ICs and result from an inflammatory pathway.

Since both central and peripheral vestibular damage seem to parallel the progression of the disease in our study, VNG and peripheral vestibular examination could be used as a method of surveillance in FD. When vestibular dysfunction is identified, especially with the pattern of: (1) a wide-spread visuo-oculomotor deficits, and (2) peripheral vestibular organ damage inconsistent with the distribution of a single VN branch or IAA, a multi-system evaluation should be conducted to early discover the damage of important organs such as heart and kidney.

Because of the limitations of sample size and non-normal distributions of part of the data in our study, some significant associations might have been missed. For example, FD can cause extensive brainstem and cerebellar dysfunction, which theoretically leads to gaze stabilizing system impairment and visual fixation disorder. However, although the incidence rate of saccadic intrusions in the patient group seemed to be higher than that in the control group, the difference was not statistically significant, which might be due to the small sample size, or might be because the characteristics of saccade intrusions in the patients are different from the normal population despite the same incidence rate, such as the frequency, duration, amplitude, and saccadic interval, which needs more detailed investigation. A multi-center study with a larger sample size and a follow-up study to get normally distributed data are needed. Besides, more research should be done to explore the correlations between the upregulated ICs and the vestibular dysfunctions to reveal the role of inflammation in the pathogenesis.

5. Conclusion

This study shows that patients with FD in China may have extensive central and peripheral vestibular dysfunctions, with the deposition of substrates in vestibular organs being a likely mechanism. Therefore, the vestibular function may reflect the burden of systemic substrates deposition and serve as a candidate clinical marker to monitor disease progression in FD.

Authors contributions

Methodology: Yinglin Leng, Yawen Zhao, Hong Zhou, Xia Ling, Guiping Zhao and Wei Zhang; Formal analysis and Writing: Yinglin Leng, Yawen Zhao; Investigation and Data curation: Yinglin Leng, Yawen Zhao and Xia Wang; Validation: Hong Zhou, Xia Ling; Con-ceptualization, Supervision, Review & Editing: Guiping Zhao and Wei Zhang. All authors have reviewed and approved the final manuscript and agreed to be accountable for all aspects of the work.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Ethics approval

The study was performed in accordance with the ethical standards of the relevant national and institutional committees on human experimentation and was approved by the Institutional Review Board of Peking University First Hospital (No. 2021 [061]; 2021[CJ1283]). The study protocol strictly followed the guidelines of the Declaration of Helsinki (Version 2013).

Consent to participate

Informed consent for all examinations was obtained from all patients or their guardians.

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Data availability statement

The authors confirm that all data supporting the results reported in this study are available from the corresponding author upon request.

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