Vestibular and Saccadic Abnormalities in Gaucher's Disease

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Abstract Gaucher's disease (GD) is a hereditary lysosomal storage disease characterized by abnormal deposition of glucocerebroside due to the enzyme glucocerebrosidase deficiency, resulting in multi-organ pathology. GD type III has a progressive neurological involvement. We studied the vestibular and saccadic abnormalities in GD type III to determine if these parameters may be useful for assessing neurological involvement. We evaluated the vestibular and saccadic responses of two siblings with genetically identified GD type III on enzyme replacement therapy. Vestibular functions were assessed with the head impulse test (HIT), vestibular evoked myogenic potentials (VEMPs), and electrical vestibular stimulation (EVS). Saccadic functions were investigated with volitional horizontal and vertical saccades to $\pm 20^\circ$. Three-dimensional head and eye movements were recorded with dual-search coils and VEMP with surface electrodes. HIT showed impaired individual semicircular canal function with halved angular vestibulo-ocular reflex (VOR) gains and absent horizontal refixation saccade. Ocular and cervical VEMPs to air-conducted clicks were absent in the older sibling, and only cervical VEMP was present in the younger sibling indicating otolithic dysfunction. EVS showed prolonged onset latency and attenuated tonic and phasic responses suggesting impaired neural conduction and vestibular function. Horizontal saccadic velocity was miniscule ($<30^\circ/\text{s}$) and

multiple back-to-back saccades with saccade-vergence interaction were utilized to minimize eye position error in the older sibling. Vertical saccades were slightly abnormal, but vergence and smooth pursuit were normal in both siblings. Our findings suggest that GD affected the vestibular nuclei in addition to the paramedian pontine reticular formation. These vestibular and saccadic abnormalities may be useful biomarkers to monitor neurological deterioration.

Introduction

Gaucher's disease has three major subtypes: Type I is a non-neuropathic form; type II is an acute infantile neuropathic form; and type III is a subacute, juvenile neuropathic form (Winkelman et al. 1983). Slow horizontal saccade also termed as "ocular motor apraxia" a hallmark of types II and III has been reported as clinical observations (Harris et al. 1999), but never studied as three-dimensional eye movements. Previously, vestibular testing of the lateral semicircular canal function showed reduced caloric response (Winkelman et al. 1983) and absent vestibular response to yaw-axis rotation (Harris et al. 1999). Measurements of vestibular and saccadic functions in GD may provide quantitative parameters that may be used to evaluate enzyme replacement therapy's efficacy in preventing further neurological degeneration.

Our study aimed to determine the vestibular and saccadic abnormalities in GD type III. We characterized the vestibular function and its conduction pathways with mechanically and electrically evoked vestibular stimuli. We used the HIT to assess individual semicircular canal function (Aw et al. 2001); air-conducted click evoked ocular and cervical VEMPs to assess the otolith functions (Taylor et al. 2011) and EVS to examine the vestibular conduction pathway

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latency, and low and high frequency response of the vestibular system (Aw et al. 2008). Ocular motor abnormalities were investigated with volitional horizontal and vertical saccades, vergence, and smooth pursuit (Fahey et al. 2008).

Methods

Subjects. Two siblings (male, age: 19, 17 years) with GD type III, treated with enzyme replacement therapy (Imiglucerase, Genzyme Therapeutics, USA) were studied. The older patient (P1) and his brother (P2) were diagnosed at age 4 and 2 by genetic identification. Hearing and brainstem auditory evoked responses were normal in both patients. The protocols were approved by our Ethics committee Sydney Local Health District Approval No: X10-0085, University of Sydney, Database No. 13076, in accordance with Helsinki II Declaration and written informed patient consents to perform this study were obtained.

Head and Eye Movement Recordings and Analysis

Three-dimensional head and binocular eye positions in response to vestibular and ocular motor tests were recorded with pre-calibrated dual-search coils (Universal, USA) in three-axes, horizontal, vertical, and torsional, while viewing a 2 mm fixation target. The search coil, target, and current stimulus signals were sampled at 1 kHz for the HIT and at 5 kHz for EVS using Labview (National Instruments, USA). Recording system resolution: horizontal/vertical = 0.1 arcminute; torsional = 0.3 arcminute. Maximum errors were <2%. The search coil signals were computed in three dimensions in rotation vectors and Euler angles as position and velocity in space/head fixed coordinates (Aw et al. 2001, 2008; Fahey et al. 2008; Weber et al. 2008).

Vestibular and Ocular Motor Tests

Head Impulse Test. HIT used high-acceleration passive head rotations at $\sim 3,000^\circ/\text{s}^2$ along the six individual semicircular canal planes to test their angular VOR. VOR gains, onset latencies, and the saccadic refixation strategies were analyzed (Aw et al. 2001; Fahey et al. 2008; Weber et al. 2008).

Ocular and Cervical Vestibular Evoked Myogenic Potentials. VEMPs were tested using Nicolet EDX (CareFusion, UK) with air-conducted clicks (0.1 ms, 135 dB peak SPL) delivered via TDH49 headphone (Taylor et al. 2011). Ocular and cervical EMGs were sampled at 10 kHz and averaged. The first negative (n1) and positive (p1)

peaks after stimulus onset, baseline to n1, and peak-to-peak amplitudes were measured. To judge an absent cervical VEMP, an average minimum level of baseline-rectified EMG of 100 μV must be present.

Electrical Vestibular Stimulation. EVS was a bilateral, bipolar 100 ms current-step at [0.9, 2.5, 5.0, 7.5] mA generated by a DS5 stimulator (Digitimer, UK) and delivered at 1/s via electrodes (Neutralect, USA) (Aw et al. 2008). Electrically evoked vestibulo-ocular reflex (eVOR) and onset latency were measured while tonic and phasic eVORs were determined with automated software (Aw et al. 2008).

Ocular Motor Test. Eye positions were recorded with dual-search coils for: (a) Saccades: subjects tracked target-steps at center and $\pm 20^\circ$ eccentric horizontally or vertically; (b) Vergence: subjects alternately viewed the target presented 15 cm or 60 cm away; (c) Smooth pursuit: subjects tracked a sinusoidal target that moved $\pm 10^\circ$ at (0.33 and 0.50) Hz (Fahey et al. 2008).

Results

The results of both patients' vestibular and ocular motor tests are summarized in Table 1.

Impaired Individual Semicircular Canal Function

The VOR gains from the HIT in all individual semicircular canals in both GD patients were reduced to a mean of 0.49 (Fig. 1a, b and Table 1), half of close to unity gain in normal subjects (Aw et al. 2001; Fahey et al. 2008; Weber et al. 2008). Head impulse latencies from all the semicircular canals were prolonged to a mean of 18 ms. Horizontal refixation saccades were absent in both patients to horizontal canal impulses, but overt and covert refixation saccades were present to anterior and posterior canal impulses (Weber et al. 2008).

Absent or Reduced Ocular and Cervical VEMP

Ocular and cervical VEMPs, which tested the otolith functions, were impaired in GD (Fig. 1c, Table 1). Ocular VEMPs were absent in both patients. Cervical VEMPs were absent in P1 in the presence average baseline-rectified EMG >100 μV . In P2, the cervical VEMP p13-n23 latencies were normal, and peak-to-peak amplitudes were at the lower limits of normal on both sides (Taylor et al. 2011).

Impaired Tonic and Phasic Responses to EVS

The eVOR latency measured with the torsional component was prolonged to 12 ms compared to normal of 9 ms (Aw et al. 2008). However, horizontal eVOR latency, which is

Table 1 Results from both Gaucher's Disease (GD) type III patients (P1, P2) to the head impulse test (HIT), ocular and cervical vestibular evoked myogenic potentials (VEMP), and electrical vestibular stimulation (EVS). The symbol (–) indicates absent response

Patient	Side	Head impulse test			
		Latency H/A/P (ms)	VOR gain		
			Horizontal	Anterior	Posterior
P1	L	21/18/19	0.38 ± 0.01	0.36 ± 0.01	0.58 ± 0.01
	R	20/16/19	0.53 ± 0.01	0.38 ± 0.01	0.57 ± 0.03
P2	L	16/18/20	0.71 ± 0.01	0.39 ± 0.01	0.35 ± 0.03
	R	14/19/20	0.81 ± 0.01	0.57 ± 0.02	0.27 ± 0.01
Ocular VEMP					
		p13 (ms)	n23 (ms)	p-p (μV)	
P1	L	–	–	–	
	R	–	–	–	
P2	L	–	–	–	
	R	–	–	–	
Cervical VEMP					
		p13 (ms)	n23 (ms)	p-p (μV)	
P1	L	–	–	–	
	R	–	–	–	
P2	L	10.8	19.0	71.7	
	R	10.7	18.9	63.3	
Electrical vestibular stimulation					
		Onset latency at 7.5 mA (ms)	Tonic eVOR (°/s) 0.9/2.5/5.0/7.5 mA	Phasic eVOR initiation (°/s ²) 0.9/2.5/5.0/7.5 mA	Phasic eVOR cessation (°/s ²) 0.9/2.5/5.0/7.5 mA
P1	L	11.4	0.49/1.53/3.74/5.38	0/187/398/702	0/232/414/448
	R	11.4	0.58/1.39/2.92/4.17	0/193/381/439	0/196/341/537
P2	L	12.2	0.28/0.63/1.74/2.73	0/119/294/424	0/158/227/329
	R	12.2	0.51/0.70/1.76/2.59	0/0/187/322	0/0/230/349

normally the same as torsional latency, was prolonged to 16 ms. Tonic eVOR was symmetrically reduced in both GD patients (typified by P1 in Fig. 1d, Table 1) while phasic eVOR initiation and cessation were attenuated to about half normal response in both patients.

Slowed Horizontal Saccades and Impaired Vertical Saccades

Visually guided volitional horizontal saccades to $\pm 20^\circ$ were severely slowed when compared to vertical saccades in both patients (Fig. 2). The horizontal saccades in P1 consisted of multiple (≥ 5) tiny back-to-back saccadic steps of ($1\text{--}2^\circ$) and peak horizontal eye velocities of between 5 and $30^\circ/\text{s}$ (Fig. 2a). P1 achieved 75% of his desired eye position with multiple saccades assisted by vergence eye movements with resulting horizontal saccadic hypometria. Small vertical and torsional saccadic eye movements present during horizontal saccades were normal. Similar multiple (≥ 5) saccades in P2 with higher peak horizontal

eye velocities of between 5 and $60^\circ/\text{s}$. P2 was able to achieve the target without saccadic hypometria and without requiring vergence because of higher peak horizontal eye velocity (Fig. 2b). Vertical saccades were also abnormal and impaired in P1 with the mean initial saccade amplitude of 12.6° with mean velocity of $211^\circ/\text{s}$, achieving 60% of target position typified by P1 in Fig. 2c. Downward saccade was more affected than upward saccade in P1. The mean latency in the P1 for horizontal saccade was 341 ms and vertical saccade was 211 ms which were similar to normal saccadic latencies. Horizontal smooth pursuit and vergence were normal in both patients (typified by P1 in Fig. 2d, e). The age-matched normal subject during either horizontal or vertical saccades to $\pm 20^\circ$ showed a large initial saccade amplitude of about 19° with peak velocity of $300\text{--}400^\circ/\text{s}$ to achieve about 95% of the desired eye position followed by a smaller saccade to acquire the target (Fig. 2f, g). The mean latency in the normal subject for horizontal saccade was 380 ms and vertical saccade was 302 ms.

Fig. 1 (a) Time series of head impulse test of horizontal, anterior, and posterior semicircular canals in Gaucher's disease (GD) type III typified by patient P1 (*older sibling*). The angular vestibulo-ocular

reflex (VOR) gains were reduced about half of normal close to unity gain. Latency of the angular VOR was prolonged to a mean of about 18 ms, twice normal latency. Despite the decline in horizontal angular

Discussion

The newer vestibular tests in this study provide quantitative measurements of the vestibular function. Vestibular abnormalities in the two GD type III patients from mechanically and electrically evoked vestibular stimuli suggest that GD also universally affects the brainstem vestibular nuclei which have been shown to suffer neuronal loss in infantile GD type II (Lacey and Terplan 1984).

Horizontal, anterior, and posterior semicircular canal functions measured with the HIT were impaired as the angular VOR gains were about half of the close to unity gain in normal subjects (Aw et al. 2001; Fahey et al. 2008; Weber et al. 2008). Onset latencies of HIT were prolonged from (7–10) ms (Aw et al. 1996) to ~18 ms. Horizontal saccadic initiation failure (Harris et al. 1999) caused the absence of horizontal refixation saccades in response to the reduced horizontal VOR gain. This precludes clinical observation of the horizontal refixation saccade in presence of deficient horizontal VOR gain (Halmagyi and Curthoys 1988). However, monitoring the head impulse test can now be done clinically using video-oculography (MacDougall et al. 2009).

Ocular VEMPs were absent in both patients and cervical VEMPs were absent in P1 and at the lower limit of normal in P2 suggesting that otolithic functions were also compromised (Taylor et al. 2011). Ocular VEMPs, which mostly screens utricular function, were more susceptible to damage than cervical VEMPs which assess saccular function (Rosengren and Kingma 2013).

EVS provides both low and high frequency stimuli to both semicircular canal and otolith pathways (Aw et al. 2008). Both tonic eVOR and phasic eVOR initiation and cessation were reduced and attenuated. The prolonged eVOR latency of 12 ms for the torsional component and 16 ms for the horizontal component compared to normal latency of 9 ms suggests a neural conduction delay. Neuronal loss in vestibular nuclei may account for both impaired vestibular response as well as the conduction delay (Lacey and Terplan 1984).

Gaucher's disease is well known to cause slow horizontal saccades due to neuronal destruction of the paramedian pontine reticular formation (Winkelman et al. 1983; Harris et al. 1999). However, the slow horizontal saccade observed clinically has never been quantitatively measured. Our

study again quantitatively measured and confirmed this horizontal saccadic slowing in GD type III (Harris et al. 1999; Benko et al. 2011). Detailed three-dimensional examination of the slowed horizontal saccades increases our understanding of deficits in the neural substrates that control saccades in GD type III (Ramat et al. 2007). When a saccade is initiated, omnipause neurons in raphe interpositus nucleus stop tonic inhibition of premotor burst neurons of horizontal saccades in paramedian pontine reticular formation and vertical saccades in the rostral interstitial nuclei of the medial longitudinal fasciculus. Synchronous bursts of horizontal, vertical, and torsional saccadic velocities in our data support the integrity of the omnipause neurons. However miniscule horizontal saccadic velocity suggests the loss of premotor burst neurons in paramedian pontine reticular formation, responsible for horizontal saccadic velocity initiation and amplitude. The neural integrator in the nucleus prepositus hypoglossi and medial vestibular nucleus may also be impaired because of the saccadic hypometria observed in P1. Multiple back-to-back saccades with saccade-vergence interaction were utilized and minimized to eye position error, which can be observed clinically as slow horizontal saccades. Disconjugate eye movements in the older sibling confirmed that the premotor commands that encoded monocular eye movement signals to lateral rectus and medial rectus separately in paramedian pontine reticular formation (Zhou and King 1998) can be affected to different extents in GD type III. Presently saccadic test used to follow-up patients on the disease progression can also be clinically measured using infrared oculography (Fahey et al. 2008). The patients also showed early vertical saccadic abnormalities evidenced by the smaller initial saccadic amplitude with lower peak velocity and only achieving about 60% of desired target position similar to responses previously reported (Benko et al. 2011). However, their horizontal and vertical saccadic latencies were normal and not prolonged.

These novel vestibular tests together with saccadic measurements might be useful as qualitative and quantitative biomarkers to monitor further central nervous system deterioration in GD patients on therapeutic enzyme replacement. The vestibular parameters such as HIT VOR gain, EVS onset latency, and VEMP peak-to-peak amplitude may be useful clinical outcome measures for clinical trials that, for example, can be correlated with their modified Rankin

VOR gain, there was absence of horizontal refixation saccades. (b) Phase-plane plots of eye velocity versus head velocity to head impulse tests of both GD patients (P1, P2) compared to normal response showing the reduction in angular VOR gain. (c) Ocular and cervical vestibular evoked myogenic potentials (VEMPs) evoked by air-conducted clicks (0.1 ms, 135 dB peak SPL) used to assess otolith functions. P1 showed absence of both ocular and cervical VEMPs

bilaterally. P2 (younger sibling) had preserved cervical VEMP at the lower limits of normal, but complete absence of ocular VEMP. (d) Tonic and phasic eVORs in response to electrical vestibular stimulation (EVS) were symmetrically reduced to about half of age-matched normal subject. Latency of eVOR was prolonged to ~12 ms for torsion (normal latency was ~9 ms), but to 16 ms for horizontal

Scale scores used for measuring the degree of disability and dependence (Patel et al. 2012). This information may then be used to manage the patient's activities of daily living such as driving a motor vehicle and occupational pursuits that require visual-vestibular interaction.

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Take-Home Message

Gaucher's disease has distinctive vestibular and eye movement abnormalities, which could be used as biomarkers of neurological involvement.

Compliance with Ethics Guidelines

Conflict of Interest

Luke Chen declares that he has no conflict of interest.

Michael J Todd declares that he has no conflict of interest.

G Michael Halmagyi is an unpaid consultant of GN Otometrics and received funding for travel related to GN Otometrics.

Swee T Aw declares that she has no conflict of interest.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation: Sydney Local Health District, Approval No: X10-0085, University of Sydney, Database No. 13076, and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

No identifying information about patients is included in the article.

Contributions of Individual Authors

Luke Chen tested the patients, analyzed their data, assisted in interpreting the data, preparing and revising the manuscript for intellectual content.

Michael J Todd designed and implemented the hardware and software for data collection and data analysis and assisted in revising the manuscript for intellectual content.

G Michael Halmagyi recruited the patients from Royal Prince Alfred Hospital, Australia, and assisted in revising the manuscript for intellectual content.

Swee T Aw designed the study, prepared and interpreted all the research data and figures. She was in charge of drafting, revising for intellectual content, and submitting the manuscript.

Guarantor

Dr SweeT Aw serves as guarantor for the article, accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Fig. 2 (a) Horizontal saccades in Gaucher's Disease (GD) type III. *P1* had more severe abnormalities because he commenced enzyme replacement therapy at age 4, while *P2* had treatment at age 2 after genetic testing following his brother's diagnosis. In *P1* during horizontal saccades, horizontal eye velocities were between 5 and 30°/s (compared to an age-matched normal horizontal saccadic eye velocities 300–400°/s). There were multiple back-to-back horizontal saccades, and he achieved 75% of his desired eye position assisted by vergence eye movements resulting in saccadic hypometria. The small

vertical and torsional saccadic eye movements were present during horizontal saccades were normal. (b) In *P2*, multiple saccades compensated for the slow horizontal saccadic eye velocity with any vergence eye movements. (c) Both patients' vertical saccadic eye movements (typified by *P1*) were slightly abnormal in position and velocity. (d) Vergence eye movements and (e) horizontal smooth pursuit were normal in both patients (typified by *P1*). (f) Age-matched normal horizontal saccades and (g) vertical saccades

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