

# Vestibular function in patients with Niemann-Pick type C disease

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**Abstract** We investigated whether vestibular dysfunction may cause or contribute to postural imbalance and falls in patients with Niemann-Pick type C disease (NP-C). Eight patients with NP-C disease and 20 healthy controls were examined using the video-based head impulse test (vHIT) and caloric irrigation to investigate horizontal canal function as well as ocular- and cervical vestibular evoked myogenic potentials (o- and cVEMP), and binocular subjective visual vertical estimation (SVV) for otolith function, and static posturography. There were no significant differences in vestibulo-ocular gain, caloric excitability, o-/cVEMP measures or SVV between the two groups. Posturographic total sway path (tSP) and root mean square (RMS) were significantly higher in NP-C than in controls in 3 out of 4 conditions. The Romberg quotient (RQ) to assess the amount of visual stabilization was significantly lower in the NP-C than in the HC group. In contrast to other inherited metabolic disorders, such as Morbus Gaucher type 3, we did not find any evidence for an impairment of canal or otolith function in patients with NP-C as their cause of postural imbalance. Since RQ was low in NP-C patients, indicating proper

sensory input, the observed increased postural sway is most likely due to a cerebellar dysfunction in NP-C, which may therefore, explain postural imbalance.

**Keywords** Metabolic disease (inherited) · Lipidoses · Niemann-Pick type C · Gait disorders/ataxia · Vertigo · Vestibular function · Vestibular evoked myogenic potentials

## Introduction

Niemann-Pick type C (NP-C) is a rare, multisystemic disease caused by pathological lipid storage and presenting with systemic, neurologic and psychiatric symptoms [1]. The cardinal symptom in all disease forms is vertical supranuclear saccade palsy, leading to complete gaze palsy in some patients, found in 70 % of patients from an international disease registry [2], but other ocular motor systems can also be impaired [3, 4]. One of the most prominent neurologic symptoms, especially in juvenile and adult forms is postural imbalance and gait disorder with recurrent falls. This may be due to impaired vestibular function, i.e., bilateral vestibulopathy (as in Morbus Gaucher type 3 [5] or chronic progressive external ophthalmoplegia [6]), cerebellar ataxia [2] or a combination of both as in cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS) [7, 8].

A vestibular deficit is plausible, because hearing is also impaired in patients with NP-C. A prior study showed high-frequency sensorineural hearing loss with retrocochlear involvement, with hearing aids required at least in later stages of the disease [9], however, in the prior sibling studies, a normal vestibulo-ocular reflex (VOR) was observed [10, 11].

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Intact function of the vestibular, proprioceptive and cerebellar systems is necessary for good balance and postural stability, which can be assessed by posturography [12]. With this tool, identification of the nature of the balance disturbance and topo-anatomical differentiation of the cerebellar impairment are possible [13].

The function of the vestibular system can be easily quantified nowadays. The angular VOR (aVOR) gain, defined as the ratio of eye velocity to head velocity, can be assessed by the video-based head impulse test (vHIT) in the high-frequency range [14] and by caloric irrigation in the low-frequency range [15]. Otolith function can be examined by ocular vestibular evoked myogenic potentials (oVEMP) for the utricle [16] and cervical VEMP for the saccule [17]. Furthermore, graviceptive pathways can be assessed by examination of the static subjective visual vertical (SVV) with the help of the bedside bucket test [18]. In this study, we systematically examined the function of the vestibular system and postural balance in a cohort of eight patients with NP-C using the abovementioned clinical tools.

## Methods

### Subjects

This study was conducted at a large tertiary outpatient clinic for vestibular and ocular motor disorders. Six patients with genetically confirmed and two patients with biochemically confirmed NP-C disease (2 females; age  $27.3 \pm 10.4$  years (mean  $\pm$  SD), range 17–51 years, mean age of onset  $9.4 \pm 4.4$  years, mean age at diagnosis  $18.4 \pm 13.8$  years, mean disease duration  $18 \pm 12.4$  years) were included. Results were compared with those of twenty age-matched healthy controls (HC) (11 females,  $28.0 \pm 10.9$ , range 11–57 years), with no history of vestibular, neuro-ophthalmologic or neurologic disease (Table 1). Clinical data of 5 out of 8 patients have been reported elsewhere [19].

### Neurological examination

All patients received a thorough neurologic, neuro-ophthalmologic and neuro-otologic examination. To evaluate the overall status of NP-C disease, the modified Disability Rating Scale (mDRS) [20, 21] was administered; cerebellar function was assessed by administration of the Scale for the Assessment and Rating of Ataxia (SARA) [22, 23]. The neurologic examination furthermore involved: examination of the cranial nerves, examination of the reflexes of the upper and lower extremities with

pyramidal signs and extremity tonus. Proprioception was assessed clinically by the tuning fork examination, with a normal finding rated as 6–8/8 and pathological proprioception rated as  $<5/8$ , and electrophysiologically by measuring somatosensory evoked potentials (SSEP) of the tibial and median nerves. Neuropsychologic status was assessed by the Montreal Cognitive Assessment [24]. All patients underwent brain magnetic resonance imaging (MRI) (Table 1).

The neuro-ophthalmologic and neuro-otologic examination comprised examination with and without Frenzel's glasses to detect nystagmus, gaze-evoked nystagmus, head-shaking nystagmus, smooth pursuit, saccades, and optokinetic nystagmus.

### Ocular and cervical vestibular evoked myogenic potentials (o/cVEMP)

We used the same methodology as the one employed in previous studies [25, 26]. For oVEMP, subjects lay in a supine position and were instructed to foveate a red dot fastened at the minishaker margin during oVEMP stimulation. Tap stimuli were delivered with a Bruel and Kjaer Mini-Shaker Type 4810 (2-ms clicks of positive polarity, with a repetition rate of 2 per second) at the midline of the hairline, 30 % of the distance between theinion and nasion. The recording electrode was positioned over the inferior oblique muscle bilaterally, approximately 3 mm below the eye and centered beneath the pupil; a reference electrode was placed on the chin and a ground electrode under the chin. The responses to 50–100 stimuli were averaged. n1 and p1 were identified as the first negative and positive peaks that occurred between 10 and 20 ms after stimulus onset [27]. For cVEMP, participants were instructed to lift their heads with active straining of the sternocleidomastoid muscles on both sides to provide tonic background muscle activity during stimulation and recording. Air-conducted 500-Hz, 100-dB SPL tone bursts were delivered monaurally via intra-auricular headphones. Cervical VEMP were recorded from an electrode montage consisting of a recording electrode placed at the midpoint of the ipsilateral sternocleidomastoid muscle belly, a reference electrode placed on the manubrium sterni, and a ground electrode placed on the forehead. p1 and n2 peaks were identified as the first positive and negative peaks that occurred between 13 and 23 ms after stimulus onset. Peak-to-peak (PP) amplitudes, calculated as the sum of p1 and n2 peaks, were then divided by mean electromyographic activity recorded after the stimulus onset to check for background muscle activity. Corrected cVEMP PP amplitudes and p1 latencies were evaluated.

**Table 1** Demographic and clinical characteristics of Niemann-Pick type C patients

Patient no./sex/age y	Age of onset/diagnosis y/disease duration	Medication	Genotype	Neurologic and psychiatric findings <sup>a</sup>	Internal manifestation/ other findings	Tibial nerve SSEP/vibration sense LE	Ocular motor findings <sup>b</sup>	MRI findings <sup>c</sup>	MoCA <sup>d</sup>	mDRS <sup>e</sup>	SARA <sup>f</sup>
1/M/24	10/21/14	Miglustat 600 mg/d, hearing devices bilateral	<i>NPC1</i> : c.2474A > G c.3160G > A	b, c, d, f, h, k, l, m, s, t, y	Splenomegaly	Prolonged latencies L > R bilateral 8/8	a, c, e, h	n	25	8	11
2/M/20	8/18/12	Miglustat 600 mg/d, risperidone 0.5 mg/d	No mutation in <i>NPC1</i> and <i>NPC2</i> genes found <sup>g</sup>	b, c, d, f, k, r, s, t	Mild hepatosplenomegaly	Prolonged latencies bilateral radial 6/8 R, 5/8 L, malleolar 6/8 R, 5/8 L	a, c, e	b	23	7	10.5
3/F/51	40/49/11	Miglustat 600 mg/d, hearing devices	<i>NPC1</i> : c.2621A > T c.2872C > T	b, c, i, k, m, s, r, t	Mild splenomegaly	NP	a, b, c, e, g, h	a	NP	6	4
4/M/28	1/1/27	Miglustat 600 mg/d, xipamid 2.5 mg/d, aliskiren 150 mg/d	<i>NPC1</i> : c.3182T > C c.3182T > C	b, c, d, f, s, t, y	Hepatosplenomegaly	N	a, c, h	a, c, d	24	5	5
5/F/17	10/11/7	Miglustat 600 mg/d vitamin D 500 I.E./d	No mutation in <i>NPC1</i> and <i>NPC2</i> genes found <sup>g</sup>	b, f, i, s, t	Splenomegaly	N	a, c, e	n	25	9	7
6/M/25/	12/17/13	Miglustat 600 mg/d, lamotrigine 350 mg/d, piracetam 3600 mg/d, ginkgo biloba	<i>NPC1</i> : c.808delG c.2861C > T	a, b, d, g, i, j, k, o, p, s, t, u, y, z	Splenomegaly	N	a, b, c, e, h	b, f	14	9	7.5
7/M/24	14/15/10	Miglustat 400 mg/d, ginkgo biloba, vitamin E, piracetam 3600 mg/d	<i>NPC1</i> : c.1723delG c.2861C > T	b, c, d, i, j, k, l, r, s, t, y, z, ac, ad, ae	Mild splenomegaly	Prolonged latencies bilateral, decreased amplitudes bilateral 5/8	b, c, d, f, h	n	18	9	10.5
8/M/29	14/15/16	Miglustat 300 mg/d, olanzapine 20 mg/d, magnesium	<i>NPC1</i> : c.2861C > G c.3433T > C	b, c, d, f, i, j, k, p, r, s, t, u, y, z, ac, ae	Splenomegaly	N	a, b, c, d, e, g, h	n	9	13	19

L left, LE lower extremities, MoCA montreal cognitive assessment, mDRS modified disability rating scale, MRI magnetic resonance imaging, N normal, NP not performed, R right, SARA scale for the assessment and rating of ataxia, SSEP somatosensory evoked potentials

<sup>a</sup> Neurologic and psychiatric findings: a = epilepsy; b = ataxic stance and gait; c = dysmetria; d = dystonia; e = contractures of Achilles tendons; f = dysphagia; g = gelastic cataplexy; h = dyskinesias; i = emotional instability/depression; j = clonus lower extremities; k = hyperreflexia; l = balbuties; m = hearing impairment; n = confined to a wheelchair; o = excessive salivation; p = hypomimia; r = organic psychosis; s = dysarthria; t = cognitive impairment; u = logorrhea; v = complete anarthria; x = developmental delay; y = tremor upper extremities; z = acatasia; aa = myoclonia; ab = hypofonia; ac = daily somnolence; ad = panic attacks; ae = verbal aggressiveness

<sup>b</sup> Ocular motor findings: a = slow vertical saccades; b = vertical saccade paresis downward; c = impaired vertical smooth pursuit; d = fixation instability, e.g., square wave jerks; e = impaired vertical optokinetic nystagmus; f = strabismus; g = slow horizontal saccades; h = impaired horizontal smooth pursuit

<sup>c</sup> MRI findings: a = supratentorial enlarged liquor spaces; b = generalized atrophy; c = cerebellar atrophy; d = brainstem atrophy; e = leukodystrophy; f = periventricular signal enhancement; n = normal findings; g = calcifications

<sup>d</sup> The total possible Montreal Cognitive Assessment (MoCA) score is 30 points; a score of 26 and higher is considered normal

<sup>e</sup> The lowest possible modified Disability Rating Scale (mDRS) score is 0 points; the highest is 24

<sup>f</sup> The lowest possible score of the Scale for the Assessment and Rating of Ataxia (SARA) is 0, the highest possible score is 40 points

<sup>g</sup> Positive Filipin Staining (variant type)

### Video-based head impulse testing (vHIT)

The aVOR gain (eye velocity/head velocity) [28], assessed by the administration of the HIT with the EyeSeeCam system [29], was evaluated. The course of VOR was visually assessed for the presence of catch-up saccades.

Eye and head movements were recorded monocularly on the left eye with 2-dimensional video-oculography (VOG) [30]. Each participant was instructed to binocularly foveate a visual target comprising a visual angle of  $0.3^\circ$  presented in the center of the 22" large computer monitor (LG, FLATRON W2242PK-SS, LG Electronics, Germany) running at 60 Hz. Monitor luminance was  $250 \text{ cd/m}^2$ . The monitor was positioned 60 cm from the participant's nasion and subtended a visual angle of  $43.2^\circ$  horizontally by  $27.7^\circ$  vertically. Eye dominance was not determined. The VOG system was calibrated for each participant by recording eye fixations at the central and eccentric positions aligned in  $8.5^\circ$  array across a range of  $\pm 15^\circ$ . Calibration recordings were visually inspected to exclude artifacts.  $10 \pm 2$  head impulses were performed to each side.

### Caloric testing

Caloric testing was performed with bithermal caloric irrigation (water temperature  $30^\circ$  and  $44^\circ$ , duration of irrigation 30 s). Patients lay in a supine position with their heads turned to the opposite ear during the measurement. Caloric-induced nystagmus was recorded for 2 min by means of the VOG system (EyeSeeCam<sup>®</sup> [29]). To calculate the slow-phase velocity (SPV) of the caloric-induced nystagmus, eye velocity was calculated using numerical three-point differentiation of eye position and subsequent Gaussian low-pass filtering with a corner frequency of 30 Hz. The high-frequency velocity peaks of nystagmus quick phases, saccades and blink artifacts were removed from eye velocity using an absolute acceleration threshold and subsequent floating median filter with a time window of 0.25 s. For robust extreme value (maximum or minimum) determination, the squared fit was calculated from the SPV data window ( $\pm 15$  s about the extrema), which was previously filtered by a zero-phase digital filter. The peak slow-phase velocity (PSPV) of the caloric-induced nystagmus was calculated as an extreme value of the fitted curve.

All patients underwent caloric irrigation; the results of the caloric testing of 3 out of 8 patients (patients no. 3, 6 and 8) were not quantitatively analyzed due to non-compliance or artifacts.

Directional preponderance was calculated using the standard Jongkees formula [27] and PSPV values  $< 5^\circ/\text{s}$  were considered pathological. The asymmetry ratio was considered abnormal when  $\geq 25\%$ .

### Subjective visual vertical (SVV)

SVV was determined by binocular estimation of the dark straight line at the bottom of the bucket which was rotated clockwise or counterclockwise. A mean of 10 measurements, exceeding the range of values  $0^\circ \pm 2.3^\circ$ , was considered a criterion for a pathological SVV tilt [18].

### Posturography

The posturographic examination was performed in the upright position with eyes open and closed, on firm ground (conditions 1 and 2) and on a slab of foam rubber (conditions 3 and 4) [12]. The total body sway (tSP) in 30 s of the posturographic measurement, expressed as the sway path values [m/min], root mean square (RMS) [mm] and frequency spectrum between 2.4 and 3.5 Hz (Fast Fourier Transform, FFT) of the  $z$  axis (head-vertical) (kgf/Hz) of the measurements were analyzed. The Romberg quotient (RQ), a ratio of the tSP with eyes closed and open, to assess the amount of visual stabilization, was calculated [31].

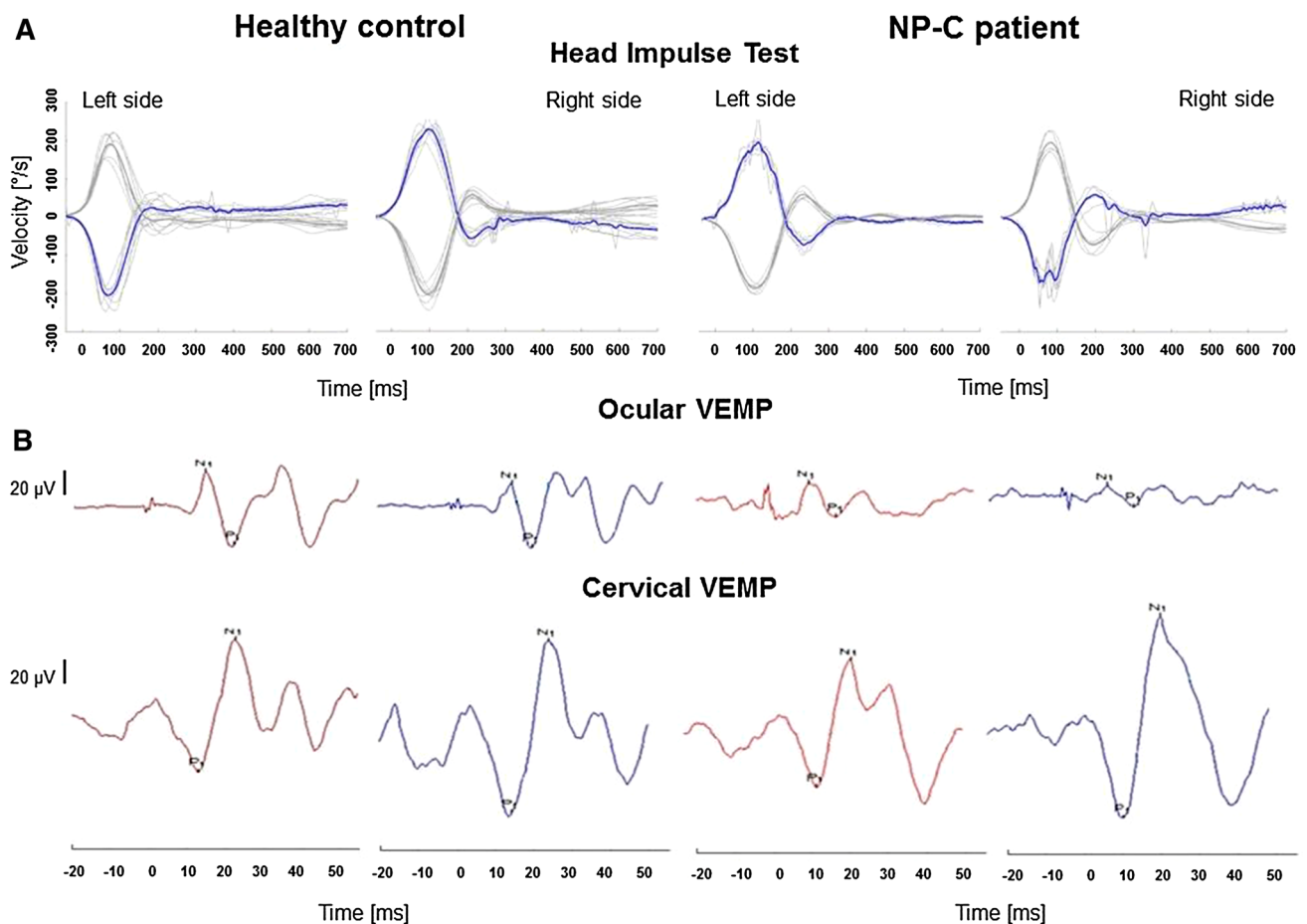
### Statistical methods

Statistical analysis and figure design were performed using SPSS version 22.0.0 (IBM, New York, NY, USA) and MATLAB (The Mathworks Inc). Differences were considered significant if  $p < 0.05$ . Normality of data distribution was tested using the mean, median, standard deviation and visual inspection of normal Q–Q plots and box plots. As data were not normally distributed, Wilcoxon related-samples rank test and non-related samples Mann–Whitney  $U$  test were conducted. To assess the relationships between tested variables, Spearman rank correlation coefficient was used. Patients who were not physically capable of performing the particular score tasks or who did not perform the test for other reasons were excluded from the analysis.

## Results

### Angular VOR

Representative raw data of a patient with NP-C and an HC subject are presented in Fig. 1a. The mean aVOR gain in patients with NP-C was  $1.07 \pm 0.12$  and in controls  $1.10 \pm 0.12$  ( $p = 0.469$ ) (Fig. 2a). There were no statistically significant relationships with other vestibular and neurologic tests (SVV:  $\rho = 0.250$ ,  $p = 0.589$ ; oVEMP n1 amplitude:  $\rho = 0.069$ ,  $p = 0.727$ ; cVEMP PP amplitude:  $\rho = 0.163$ ,  $p = 0.408$ ; SARA:  $\rho = -0.198$ ,  $p = 0.670$ ; mDRS:  $\rho = 0.146$ ,  $p = 0.729$ ). There was also no



**Fig. 1** Angular vestibulo-ocular reflex, ocular and cervical vestibular evoked myogenic potentials in a patient with Niemann-Pick type C and a control. Representative raw traces of the angular vestibulo-ocular reflex (aVOR) (a), ocular and cervical vestibular evoked myogenic potentials (o- and cVEMP) (b) of a patient with Niemann-

Pick type C (patient no. 5) and a healthy control. The *blue line* (a) represents the mean of performed video-based head impulse tests (vHIT). The *red line* (b) indicates the function of the otolith organs on the left side, the *blue line* of those on the right side

correlation with age ( $p = 0.157$ ,  $p = 0.426$ ), disease duration ( $p = 0.405$ ,  $p = 0.320$ ) or age of onset ( $p = 0.217$ ,  $p = 0.606$ ).

### Caloric irrigation testing

Mean PSPV of caloric-induced nystagmus was  $18.5 \pm 6.8^\circ/s$  in response to warm water and  $12.6 \pm 5.3^\circ/s$  in response to cold water. After excluding the patient who suffered a left labyrinth contusion with bleeding in 2008 after a bike accident with a left-side canal paresis with PSPV of  $2^\circ/s$  (patient no. 6), the asymmetry ratio was  $10 \pm 1.6\%$ .

### Ocular and cervical VEMP

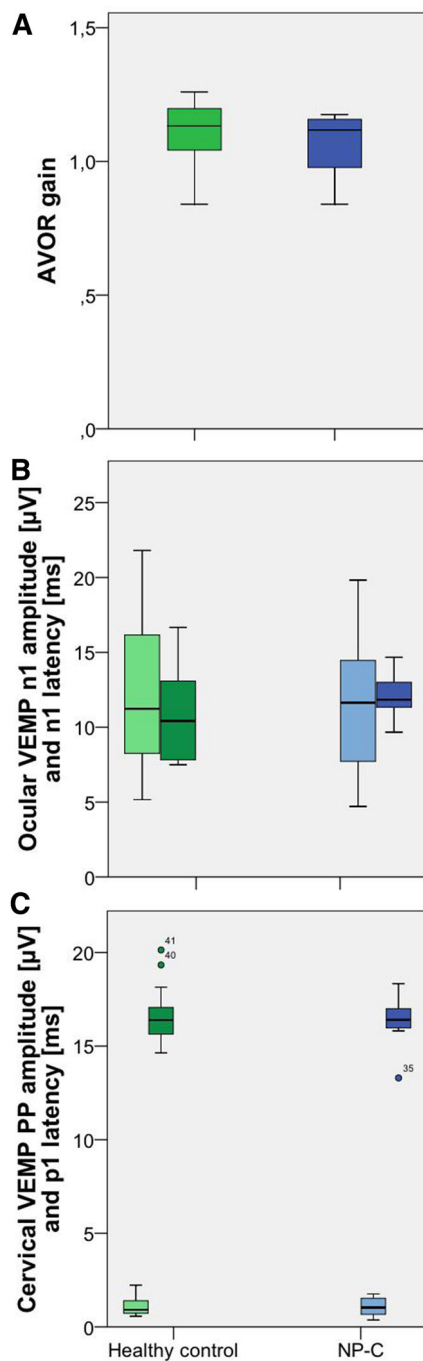
Representative raw data of the NP-C and HC subjects are presented in Fig. 1b. Mean oVEMP n1 amplitude was  $11.5 \pm 5 \mu V$  in NP-C and  $12.0 \pm 4.8 \mu V$  ( $p = 0.784$ ) in HC groups. Mean oVEMP n1 latency was  $12.1 \pm 1.5$  ms in NP-

C patients and  $10.8 \pm 3.1$  ms ( $p = 0.199$ ) in HC subjects. Mean corrected cVEMP PP amplitude was  $1.07 \pm 0.5 \mu V$  in NP-C and  $1.1 \pm 0.5 \mu V$  in HCs ( $p = 0.862$ ). Mean cVEMP p1 latency was  $16.3 \pm 1.4$  ms in NP-C and  $16.6 \pm 1.4$  ms in HC groups ( $p = 0.980$ ) (Fig. 2b, c).

Correlation analysis also showed no significant relationships between age of onset (oVEMP n1 amplitude:  $\rho = -0.639$ ,  $p = 0.088$ ; n1 latencies:  $\rho = -0.012$ ,  $p = 0.977$ ; cVEMP PP amplitudes:  $\rho = -0.566$ ,  $p = 0.143$ ; p1 latencies:  $\rho = 0.446$ ,  $p = 0.268$ ) and o- and cVEMP amplitudes and latencies, as well as duration of disease (oVEMP n1 amplitudes:  $\rho = 0.190$ ,  $p = 0.651$ ; n1 latencies:  $\rho = 0.262$ ,  $p = 0.531$ ; cVEMP PP amplitudes:  $\rho = 0.190$ ,  $p = 0.651$ ; p1 latencies:  $\rho = -0.238$ ,  $p = 0.570$ ) and o- and cVEMP amplitudes and latencies.

There was no relation between neurological status, as assessed by mDRS and SARA and o-/cVEMP parameters in NP-C patients (mDRS: oVEMP n1 amplitude:  $\rho = -0.586$ ,  $p = 0.127$ , n1 latency:  $\rho = -0.073$ ,  $p = 0.863$ ; cVEMP PP





**Fig. 2** Angular vestibulo-ocular reflex, ocular and cervical vestibular evoked myogenic potentials amplitudes and latencies in patients with Niemann-Pick type C and controls. Box plot representation of the angular vestibulo-ocular reflex (aVOR) gain (a), ocular vestibular evoked myogenic potentials (oVEMP) n1 amplitudes and n1 latencies, respectively, (b) and cervical VEMP peak-to-peak (PP) amplitudes and p1 latencies (cVEMP) (c) in patients with Niemann-Pick type C disease (NP-C) and healthy controls (HC). The light green depicts the VEMP amplitudes in HC, the dark green depicts the latencies in HC. The light blue depicts the VEMP amplitudes in NP-C and the dark blue depicts the VEMP latencies in NP-C. No statistically significant differences between the NP-C and HC groups were found for the vestibular measurements. The length of the boxes indicates the interquartile space (P25–P75); the horizontal line into the box represents the median (P50) and the whiskers indicate the adjacent values. The circles indicate the outliers

amplitudes:  $\rho = -0.488, p = 0.220$ , p1 latency:  $\rho = 0.610, p = 0.108$ ; SARA: oVEMP n1 amplitude:  $\rho = -0.419, p = 0.301$ , n1 latency:  $\rho = -0.299, p = 0.471$ ; cVEMP PP amplitudes:  $\rho = -0.275, p = 0.509$ , p1 latency:  $\rho = 0.575, p = 0.136$ ).

**Subjective visual vertical**

SVV was tilted in three out of eight patients with NP-C. The mean SVV was  $-0.18 \pm 2.9$  [95 % CI for the mean)

$-2.87$  to  $+2.51$ ] and was thus slightly higher than the range described previously [18]. There was no significant relationship with any of the tests.

**Posturography**

An overview of the posturographic results of all subjects can be found in Table 2.

*Condition 1 (standing on firm ground with eyes open)*  
 The tSP was  $1.8 \pm 0.7$  (1.2–2.4) m/min in NP-C patients [mean  $\pm$  SD, (95 % CI for the mean)] and  $0.7 \pm 0.1$  (0.7–0.8) m/min in controls ( $Z = -3.818, p = 4.5 \times 10^{-6}$ ) (difference: 1.1 m/min), the RMS was  $12.5 \pm 5.2$  (7.7–17.3) mm in NP-C patients and  $4.9 \pm 1.9$  (4.0–5.8) mm in controls ( $Z = -3.375, p = 2.117 \times 10^{-4}$ ) (difference: 7.6 mm). The integral of the frequency spectrum (FFT Z) was  $36.9 \pm 41.6$  (–1.6–75.4) kgf/Hz in NP-C patients and  $7.3 \pm 3.5$  (5.6–8.9) kgf/Hz in controls ( $Z = -1.881, p = 0.06$ ).

*Condition 2 (standing on firm ground with eyes closed)*  
 The tSP was  $1.8 \pm 0.7$  (1.1–2.4) m/min in NP-C patients and  $0.9 \pm 0.1$  (0.8–1) m/min in controls ( $Z = -3.818, p = 4.504 \times 10^{-6}$ ) (difference: 0.9 m/min), the RMS was  $9.4 \pm 5.1$  (4.7–14.1) mm in NP-C patients and  $5.2 \pm 1.9$  (4.0–6.1) mm in controls ( $Z = -2.434, p = 0.013$ ) (difference: 4.2 mm). The FFT Z was  $19.4 \pm 18.9$  (1.9–36.9) kgf/Hz in NP-C patients and  $6.1 \pm 1.8$  (5.3–7) kgf/Hz in controls ( $Z = -3.150, p = 0.002$ ).

*Condition 3 (standing on foam with eyes open)* The tSP of NP-C patients yielded  $3.8 \pm 2.8$  (1.3–6.4) m/min and the tSP of controls  $1.2 \pm 0.3$  (1.1–1.3) m/min (difference: 2.6 m/min) ( $Z = -2.43, p = 1.486 \times 10^{-4}$ ). The RMS was  $20 \pm 6.6$  (13.9–26.1) mm in NP-C patients and  $8.3 \pm 2.7$  (7  $\pm$  9.6) mm in controls (difference: 11.7 mm) ( $Z = -3.486, p = 1.013 \times 10^{-4}$ ). The FFT Z was  $123.1 \pm 131.5$  (1.4–244.7) kgf/Hz in NP-C patients and  $33 \pm 12.8$  (27–39) kgf/Hz in controls ( $Z = -1.771, p = 0.077$ ).

**Condition 4 (standing on foam with eyes closed)** The tSP of NP-C patients yielded  $4.8 \pm 2.5$  (2.5–7.2) m/min and in controls  $3.3 \pm 1$  (2.8–3.7) m/min (difference: 1.5 m/min) ( $Z = -1.439$ ,  $p = 0.162$ ). The RMS was  $24.9 \pm 7.6$  (17.9–32) mm in NP-C and  $19.6 \pm 27$  (16.2 ± 22.9) mm in controls (difference: 5.5 mm) ( $Z = -1.605$ ,  $p = 0.109$ ). The FFT  $Z$  was  $132.8 \pm 93.8$  (46.1–219.5) kgf/Hz in NP-C patients and  $98.2 \pm 42.6$  (77.6–118.7) kgf/Hz in controls ( $Z = -0.665$ ,  $p = 0.506$ ).

The amount of visual stabilization, as assessed by the RQ on both firm ground and foam was significantly different across the groups, being higher in controls (firm ground: NP-C  $1.01 \pm 0.24$  (0.8–1.2), HC  $1.27 \pm 0.25$  (1.2–1.4)  $p = 0.022$ ; foam: NP-C  $1.4 \pm 0.6$  (0.9–1.9), HC  $2.7 \pm 0.8$  (2.4–3.1),  $p = 2.117 \times 10^{-4}$ ).

In one patient, discrete cerebellar 3 Hz postural sway was seen (patient no 4. in Table 1). This finding has a morphological correlate in a cerebellar atrophy, as seen in MRI.

The frequency plot of an NP-C patient, a patient with a cerebellar 3-Hz sway and a healthy subject are shown in Fig. 3a, and a graphical representation of the tSP and RMS values are presented in Fig. 3b.

### Correlation analyses

There was no significant association between neurologic status, as assessed by mDRS and SARA, and posturographic parameters in NP-C patients (mDRS: tSP in condition 1:  $\rho = 0.296$ ,  $p = 0.518$ , RMS:  $\rho = 0.074$ ,  $p = 0.875$ ; tSP in condition 2:  $\rho = 0.222$ ,  $p = 0.632$ ; RMS:  $\rho = 0.667$ ,  $p = 0.102$ , tSP in condition 3:  $\rho = -0.037$ ,  $p = 0.937$ , RMS:  $\rho = 0.259$ ,  $p = 0.574$ ; tSP in condition 4:  $\rho = -0.074$ ,  $p = 0.875$ , RMS:  $\rho = 0.185$ ,  $p = 0.691$ ; SARA: tSP in condition 1  $\rho = 0.559$ ,  $p = 0.192$ , RMS:  $\rho = 0.721$ ,  $p = 0.068$ ; tSP in condition 2:  $\rho = 0.126$ ,  $p = 0.788$ ; RMS:  $\rho = 0.631$ ,  $p = 0.129$ , tSP in condition 3  $\rho = -0.180$ ,  $p = 0.699$ , RMS:  $\rho = 0.487$ ,  $p = 0.268$ ; tSP in condition 4:  $\rho = -0.595$ ,  $p = 0.159$ , RMS:  $\rho = 0.523$ ,  $p = 0.229$ ).

No significant relationships between the posturographic and VEMP parameters, but one (tSP value in condition 4 and cVEMP PP amplitudes) were seen (oVEMP n1 amplitude: tSP in condition 1:  $\rho = 0.170$ ,  $p = 0.397$ , RMS:  $\rho = 0.192$ ,  $p = 0.338$ ; tSP in condition 2:  $\rho = -0.036$ ,  $p = 0.858$ ; RMS:  $\rho = -0.125$ ,  $p = 0.536$ , tSP in condition 3:  $\rho = 0.148$ ,  $p = 0.462$ , RMS:  $\rho = 0.191$ ,  $p = 0.340$ ; tSP in condition 4:  $\rho = 0.001$ ,  $p = 0.998$ , RMS:  $\rho = 0.155$ ,  $p = 0.440$ ; cVEMP PP amplitudes: tSP in condition 1:  $\rho = -0.001$ ,  $p = 0.998$ , RMS:  $\rho = 0.018$ ,  $p = 0.930$ ; tSP in condition 2:  $\rho = -0.150$ ,  $p = 0.455$ ; RMS:  $\rho = -0.270$ ,  $p = 0.172$ , tSP in condition 3:  $\rho = 0.015$ ,  $p = 0.940$ , RMS:

$\rho = 0.051$ ,  $p = 0.799$ ; tSP in condition 4:  $\rho = -0.384$ ,  $p = 0.048$ , RMS:  $\rho = -0.281$ ,  $p = 0.155$ ).

### Discussion

The major findings of this study are as follows: first, we did not find any evidence for an impairment of angular VOR function (in either the high-frequency or in the low-frequency range) or otolith function (in either the utricle or the saccule); second, patients showed remarkable postural instability compared with normal subjects; third, analysis of the posturographic findings indicated diffuse cerebellar disturbance with potential involvement of the vestibulo-cerebellum. Based on our results, vestibular horizontal canal and otolith function is intact.

These findings were unexpected in light of the fact that the vestibular system is commonly affected in neurodegenerative disorders [32, 33]. In fact, in another lysosomal storage disease, Gaucher disease type 3 (neuronopathic type, GD3), impaired otolith pathways and aVOR deficits with absent horizontal refixation saccades were described [5]. This might be explained by the neuronal loss and functional disturbance of the vestibular nuclei in the medulla and paramedian pontine reticular formation (PPRF), respectively, leading to horizontal saccade palsy in GD3 disease. Vestibular nuclei and their afferent and efferent projections seem to be functionally intact in NP-C disease. NP-C is a chronic progressive disease with a relatively slow progressive rate, which might explain the lack of vestibular involvement, also seen in acute cerebellar disturbance caused by a stroke or cerebellitis [34, 35]. Vestibular regions analogous to the ocular motor nuclei and supranuclear structures for gaze-holding, such as the interstitial nucleus of Cajal (INC), or the nucleus prepositus hypoglossi (NPH), and centers for horizontal saccades are relatively spared by the disease process, nevertheless, as the disease progresses, these structures might also degenerate at more severe stages of the disease. Thus, the specific pattern of impairment in NP-C and GD3 diseases suggests a different neuronal susceptibility to the toxic effects of the storage material, probably based on their biochemical properties. For instance, downward saccades are often more impaired than upward saccades in NPC disease [36]. This might be explained by a calretinin-positive excitatory input to motor centers mediating upgaze, arising from premotor centers, such as the INC, the rostral interstitial nucleus of the medial longitudinal fascicle (riMLF) and y-group [37–39]. Calretinin is a calcium-binding protein, but its functional significance is yet unclear. We can speculate whether it contributes to an improvement of the lipid storage in upward neurons, since there is a well-known calcium dyshomeostasis in patients with NP-C [40].

**Table 2** Posturographic results in Niemann-Pick type C patients and healthy controls

Group <sup>a</sup>	N <sup>b</sup>	Condition 1 <sup>c</sup> tSP (m/min)	Condition 1 RMS (mm)	Condition 1 FS FFT Z (kgf/Hz)	Condition 2 <sup>d</sup> tSP (m/min)	Condition 2 RMS (mm)	Condition 2 FS FFT Z (kgf/Hz)	Condition 3 <sup>e</sup> tSP (m/min)
NP-C	7	1.8 (0.7)	12.5 (5.2)	36.9 (41.6)	1.8 (0.7)	9.4 (5.1)	19.4 (18.9)	3.8 (2.8)
		1.7 (1.1)	13 (7.8)	19.6 (54.8)	1.6 (1.5)	9.3 (6.8)	10.8 (18.3)	3.1 (1.8)
HC	20	0.7 (1.1)	4.9 (1.9)	7.3 (3.5)	0.9 (1.4)	5.2 (1.9)	6.1 (1.8)	1.2 (0.3)
		0.8 (0.2)	4.3 (2.6)	6.3 (3.2)	0.8 (0.2)	4.8 (2.1)	5.9 (2.3)	1.2 (0.2)
P value		4.504 × 10 <sup>-6</sup>	2.117 × 10 <sup>-4</sup>	0.06	4.504 × 10 <sup>-6</sup>	0.013	0.002	1.486 × 10 <sup>-4</sup>
Group <sup>a</sup>	Condition 3 RMS (mm)	Condition 3 FS FFT Z (kgf/Hz)	Condition 4 <sup>f</sup> tSP (m/min)	Condition 4 RMS (mm)	Condition 4 FS FFT Z (kgf/Hz)	RQ <sup>g</sup> Firm ground	RQ Foam	
NP-C	20 (6.6)	123.1 (131.5)	4.8 (2.5)	24.9 (7.6)	132.8 (93.8)	1.02 (0.24)	1.42 (0.55)	
	21.6 (9.7)	101.8 (97.1)	4.7 (3.8)	27.7 (10.3)	100.7 (168)	0.96 (0.47)	1.41 (0.68)	
HC	8.3 (2.7)	33 (12.8)	3.3 (1)	19.6 (7.1)	98 (42.6)	1.27 (0.25)	2.75(0.83)	
	7.8 (3.9)	29.5 (16.3)	3.3 (1.5)	18.2 (10.9)	96 (72.3)	1.26 (0.33)	2.7 (1.51)	
P value	1.01 × 10 <sup>-4</sup>	0.077	0.162	0.116	0.506	0.022	2.117 × 10 <sup>-4</sup>	

HC healthy controls, IQR interquartile range, FFT Z Fast Fourier Transform of the z axis, FS frequency spectrum, RQ Romberg quotient, tSP total Sway Path, RMS root mean square

<sup>a</sup> Parameters are depicted as mean (standard deviation) and median (interquartile range)

<sup>b</sup> All patients, but one (patient no. 7) underwent posturographic measurements

<sup>c</sup> Standing on firm ground with eyes open

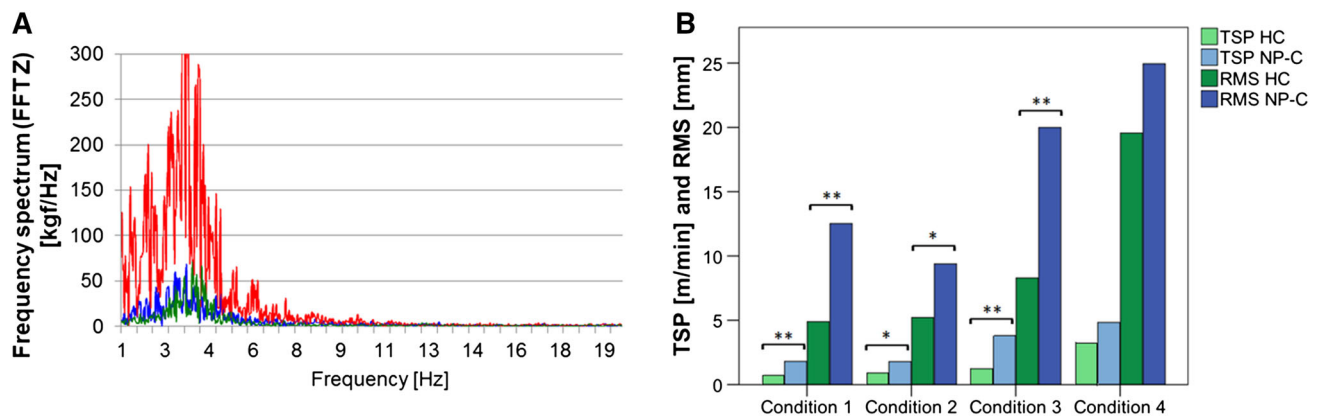
<sup>d</sup> Standing on firm ground with eyes closed

<sup>e</sup> Standing on foam with eyes open

<sup>f</sup> Standing on foam with eyes closed

<sup>g</sup> Romberg quotient (RQ)—a ratio of the total sway path with eyes closed to eyes open





**Fig. 3** Posturographic results in patients with Niemann-Pick type C and healthy controls. Frequency plot of the z axis (kgf/Hz) in a patient with Niemann-Pick type C (NP-C) (blue line), a patient with cerebellar sway (red line) and a normal subject (green line) standing on foam with eyes closed (a). Note that the frequency pattern of the NP-C patient is not significantly different from that of a healthy

subject with a normal frequency distribution. Bar representation of the differences in total sway path (TSP) and root mean square (RMS) values in patients with Niemann-Pick type C and healthy controls (b). Asterisk indicates significant difference at the 0.05 level. Double asterisk indicates significant difference at the 0.001 level

The lack of this input in downgaze pathways might explain the accentuated downgaze deficits in NP-C disease [41]. In addition, a lack of correlation between any of the vestibular tests and clinical rating scales also supports the intactness of the vestibular organs.

In terms of posturography, we found that patients with NP-C had increased body sway compared with controls in three out of four conditions. Disturbance of the somatosensory input in condition four led to an equal increase of the total sway path in both groups. The effect of vision was significantly more pronounced in controls, since the Romberg quotient was significantly higher in controls than in patients with NP-C. This finding also indicates the functionally intact vestibular organs, as visual cue is known to be of high importance in peripheral vestibulopathy to compensate for the vestibular loss [12, 42]. Moreover, due to the saccadic deficits, motor performance and orientation in space that require visual-vestibular interaction in patients with NP-C are impaired. It is likely that the balance network compensates for these ocular deficits by enhancing the other sensory input, especially vestibular and somatosensory input. Balance is not based on a fixed set of equilibrium reflexes but on a flexible, functional motor skill that can adapt with training and experience, and presumably reflects noise and regulatory activity within afferent-efferent control loops, which are plastic enough to compensate for the existing deficits.

Visual stabilization had no remarkable influence on the postural stability, as indicated by the low Romberg quotient of the total sway path in patients with NP-C, even though the proprioception was diminished in three patients. A low proportion of visual stabilization suggests that the spino-cerebellum and its spinal afferents are not primarily affected by the disease process. Nevertheless, atrophy of

the cerebellar vermis in severe cases of NP-C disease has been previously described [43, 44].

In the frequency analysis, there was no consistent 3 Hz anteroposterior cerebellar sway in patients with NP-C. One patient with cerebellar atrophy in MRI had increased postural sway at 2–3 Hz frequency, but he did not reach values seen in patients with anterior lobe lesions [13].

On the whole, the constellation of the posturographic findings (pathological sway parameters with poor visual stabilization without 3 Hz sway) suggests a rather diffuse cerebellar disturbance with a possible involvement of the vestibulo-cerebellum, rather than isolated impairment of the spino-cerebellum, anterior lobe or cerebellar hemispheres [13, 45].

In contrast, a patterned degeneration of the Purkinje cells from anterior to posterior, with surviving Purkinje cells in lobules IX and X at the terminal stages of the disease has been described in an NP-C mouse model [46]. Our NP-C cohort was relatively young (mean age  $\pm$  SD 27.3  $\pm$  10.4 years) with a rather mild cerebellar disturbance (mean SARA score 9.3/40) and lacking severe involvement of any circumscribed region of the cerebellum. Thus, the pattern of neurodegeneration described in the mouse model could not be observed.

The isolated cerebellar impairment without vestibular involvement is also in line with previously shown increased metabolism in the vestibulo-cerebellum in a rat model of peripheral vestibulopathy under therapy with acetyl-DL-leucine [47]. The beneficial effect of this therapy was seen recently in a cohort of 12 NP-C patients [19], improving stance and gait, diadochokinesis and diminishing the intensity of the square wave jerks, indicating a stabilizing effect on impaired cerebellar Purkinje cells, similar to the effect on neurons of medial

vestibular nucleus in an unilateral-vestibular-loss guinea-pig model [48]. This study has some limitations. First, the sample size is small, given that the NP-C disease is an orphan disease, meaning that this study might be underpowered. Second, as patients become fatigued very quickly, some tests were not performed due to the lack of compliance or due to physical disability or cognitive impairment. Third, there is an ongoing discussion about the sensitivity and specificity of VEMP investigation, principally because of its high interindividual, but also interrater variability [49].

#### Compliance with ethical standards

**Ethical standards** The study was performed in accordance with the Helsinki II Declaration and was approved by the ethics committee of the Ludwig-Maximilians University Medical Faculty (No. 379-12). All participants gave their informed consent prior to their inclusion in the study.

**Conflicts of interest** T.B. received honoraria for lecturing from Actelion. S.K. and S.B. have nothing to report. J.R. received speaker's honoraria from BioMarin, Shire, Genzyme and Actelion. M.S. is Joint Editor-in-Chief of the *Journal of Neurology*, Editor-in-Chief of *Frontiers of Neuro-otology* and Section Editor of *F1000*. He received speaker's honoraria from Abbott, Actelion, UCB, GSK, TEVA, Heel, Biogen, Pierre-Fabre, Eisai and Hennig Pharma. He also works as a consultant for Abbott, Heel, Synthron and Actelion.

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