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OTOLOGY

Vestibular function in panic disorder patients: a vestibular-evoked myogenic potentials and video head impulse test study

G. Angov[1] · E. Mihaylova-Angelova[2] · D. Petrova[3] · Katerina Stambolieva[4]

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Abstract

Purpose To evaluate the function of the utriculus and sacculus and their central connections by ocular and cervical vestibular-evoked myogenic potentials (oVEMPs and cVEMPs), and the function of high-frequency VOR of the semicircular canals by video head impulse test (vHIT) in patients with panic disorder (PD).

Methods Forty-eight patients with PD (21 with agoraphobia) and 20 sex- and age-matched healthy controls took part in the investigation. The vestibulo-ocular reflex (VOR) gains and latencies and peak-to-peak amplitudes of sound-induced VEMPs were measured and compared with those of healthy controls.

Results Any statistical differences in the parameters of cVEMP and oVEMP responses between both PD patients groups and between patients and healthy controls were not observed. Also, significant differences between VOR in patients and healthy controls were not found. The VOR gain, bilaterally in the three semicircular canals was within normal limits (0.8–1.2) for 67%, and higher for 33% of the patients with PD. Overt and covert saccades were not observed. The relationship between higher VOR gains and the increase of postural instability when a sensory conflict exists (standing on foam pad with eyes closed) for patients with PD was established.

Conclusion The VEMPs and vHIT tests demonstrated that there is no evidence of hypofunction of the semicircular canals in the high-frequency spectrum of VOR functioning. Nor are there any indications of impairment of the otolith system in patients with PD, regardless of their subjective vestibular sensations. The findings of the current study confirm the proposed link between anxiety, panic symptoms and postural instability in PD patients.

Keywords Panic disorder · Vestibular-evoked myogenic potentials (VEMPs) · Video head impulse test (vHIT) · Dizziness · Vestibular disturbance

Introduction

Panic disorder (with or without concomitant agoraphobia) is a relatively common and severe illness with a high degree of subjective distress, occupational and social disability [1]. About 50–90% of patients with panic disorder report experiencing dizziness. According to the DSM-V criteria, dizziness and unsteadiness are among the 13 cardinal symptoms of panic attacks [2]. The cause of panic disorder is unknown. There are two main hypotheses explaining the relationship between panic attacks and vestibular disturbances. The first is a somatopsychic impairment in which a primary inner ear disturbance causes anxiety and panic attacks. The second is a psychogenic vestibular disturbance in which patients have normal vestibular tests [3]. Panic disorder should be differentiated from phobic postural vertigo (PPV), described by Th.Brandt, who defined PPV as a syndrome of subjective

✉ Katerina Stambolieva
katerina_stambolieva@yahoo.com

1 Clinic of Neurology, Medical University, UMHAT "Alexandrovska", St. Georgy Sofiyski Str. 1, Sofia, Bulgaria

2 Medical University, UMHAT "Alexandrovska", Clinic of Child Psychiatry "St. Nikolas", St. Georgy Sofiyski Str. 1, Sofia, Bulgaria

3 Department of Neurology, National Transport Hospital "Tzar Boris III", Knyaginya Mariya-Luiza Blvd. 108, Sofia, Bulgaria

4 Department of Cognitive Psychophysiology, Institute of Neurobiology, Bulgarian Academy of Sciences, Acad. Georgi Bonchev Str. 23, 1113 Sofia, Bulgaria

unsteadiness and illusory perturbations of posture, frequently accompanied by anxiety and autonomic arousal, and defined the important characteristics for positive identification of PPV [4].

Vestibular disturbances were first observed in 60–75% of patients with panic disorder by Jacob et al. [5], by conducting a standardized neurotological battery of tests (positional, caloric, rotational, posturography, and audiologic tests). A similar neurotological battery of tests was employed in other studies on the vestibular function in patients with panic disorder, in which a higher prevalence of peripheral vestibular dysfunction of those subjects was found [6–12]. An interesting finding was the increased VOR gains in patients during rotation at low frequencies [13, 14]. Swinson et al. [14] studied 15 patients with panic disorder with prominent dizziness, and 10 healthy controls, using electronystagmography, caloric, audiologic testing, and pseudo-random rotational testing (0.32–3.25 Hz). The authors did not detect abnormalities in electronystagmography, audiological and caloric testing. However, they found that PD patients showed a higher VOR gain during rotation in the dark, compared with healthy controls. Another interesting finding was the high prevalence of migrainous vertigo among the patients with PD reported by Teggy et al. [15]. They investigated 52 patients with PD with agoraphobia, 30 without agoraphobia and 20 with depressive disorders, and did not find spontaneous nystagmus in any of the patients. The authors found a high frequency of migraine in most of the patients. Twenty patients showed unilateral caloric hyporeflexia, and 18 of them (90%) fulfilled the criteria for diagnosis of migrainous vertigo. The authors suggested that the migrainous vertigo was the most common causal factor for vestibular disorders.

Most studies have used vestibular tests (caloric and rotational) for the examination of the VOR function in the low-frequency spectrum. There is one study which examines the function of the otolith system by means of off-vertical axis rotation (OVAR) [13].

Two methods have been used in recent years for investigating each part of the peripheral vestibular apparatus: vestibular-evoked myogenic potentials (VEMPs) for testing the sacculus and the utriculus and their central connections [16–18], and video head impulse test (vHIT) for examining the high-frequency vestibulo-ocular reflex (VOR) during rapid head movement, thus evaluating the function of the semicircular canals by measurement of the eye/head gain [19].

The vHIT is a technique used to diagnose the reduction of the VOR in one side. The vHIT test is similar to the rotational test, but it examines the high-frequency VOR during rapid head movement and evaluates the function of all six semicircular canals and their nerves [19–21].

VEMPs are electrophysiological tests in which the functions of the utriculus, sacculus, and their central connections are analyzed. The cervical vestibular-evoked myogenic potentials (cVEMPs) evaluate the vestibulo-spinal pathway which starts from the saccule, passes through the inferior vestibular nerve, vestibular nucleus, medial, lateral vestibulo-spinal tract, and ends in the ipsilateral sternocleidomastoid muscle (SCM). cVEMPs detect pathologies in the inferior vestibular nerve, while ocular vestibular-evoked myogenic potentials (oVEMPs) evaluate the vestibule-ocular pathway starting from the utricle, passing through the superior vestibular nerve, vestibular nucleus, the medial longitudinal fasciculus, oculomotor nuclei, and ending in the contralateral extraocular muscles. oVEMPs detect pathology in the superior vestibular nerve [16–18, 22].

These two methods have been used in analyzing the vestibular function in a number of vestibular disorders, such as Ménière's disease [23, 24], vestibular neuritis [25], vestibular migraine [26], BPPV [27], and central vestibular disorders [28], where the VEMPs and vHIT tests are abnormal.

There is no information in the available scientific literature regarding the use of VEPMs and vHIT tests in examining the vestibular function of patients with panic disorder. This fact motivated us to evaluate the function of each part of the vestibular system in PD patients by means of VEMPs and vHIT tests.

Materials and methods

Subjects

Forty-eight consecutive patients with panic disorder (16 men and 32 women, mean age 34.4 ± 7.8), and 20 sex- and age-matched healthy controls (10 men and 10 women, mean age 31.5 ± 6.4) without any vestibular or psychiatric dysfunction, took part in the investigation. The patients with PD were consecutively recruited for 8 months at the outpatient facilities of Alexandrovska University Hospital. The patient selection was based on the following criteria: (1) confirmation of panic disorder (PD) by a senior clinical psychiatrist by means of a clinical interview, according to the DSM-V criteria; (2) aged between 18 and 50 years; (3) presence of dizziness not solely during panic attacks (from 1 week to 1 month before the visit); (4) lack of clinical history of vestibular disorders such as vestibular neuritis, Meniere's disease, bilateral vestibulopathy, vestibular migraine or head injury, which could lead to tests' abnormalities; (5) normal or medically controlled blood pressure.

Twenty-one patients (43.8%) had agoraphobia (6 men and 15 women, mean age 32.21 ± 5.3) and 27 patients (56.2%) were with PD without agoraphobia (11 men and 16 women, mean age 3.21 ± 5.3). The duration of the disease of both patient groups (with and without agoraphobia) was between 2 and 24 months. Only 17% of all

patients (8 subjects, 4 of them with agoraphobia) had been suffering from PD for over 12 months (mean duration of 20.4 ± 3.3 months); the remaining 83% had an average disease duration of 6.8 ± 3.6 months (patients with agoraphobia—5.7 ± 3.1). All patients reported a frequency of 1–2 panic attacks per week.

All participants in the study were volunteers, who participated free of charge and gave their written consent to be examined by filling in a form approved by the local Ethics Committee, and in accordance with the ethical standards of the Helsinki Declaration.

The participants were previously instructed not to take any psychiatric and/or neurotological medications 1 week before the investigation and to refrain from alcohol for 24 h before the investigation.

Measurements

The clinical history of the examined subjects was taken by means of a specially developed questionnaire based on the International Classification of Vestibular Disorders [29], concerning any history of vertigo (spontaneous or triggered), dizziness (spontaneous or triggered), vestibulo-visual and postural dysfunctions. The diagnostic criteria of the Committee for Classification of Vestibular Disorders of the Barany Society regarding vestibular migraine were used to exclude participants with migraine [30].

Before conducting the vHIT and VEMP tests, all participants underwent a full neurotological examination including:

- Videonystagmography (VNG)—for the registration of spontaneous nystagmus (sitting position with gaze straightforward), positional nystagmus (supine position, with the head held straight, head turned to the left and to the right), positioning nystagmus (during Dix-Hallpike maneuvers), gaze-evoked nystagmus and nystagmus provoked by vibration [31], head shaking and hyperventilation, saccadic test, and slow pursuit eye movement test [32, 33].
- Static posturography—for analyzing the maintenance of posture, evaluated by the length of the trajectory of the displacement of the center of foot pressure (COP) in the area under the soles, named "Sway Path" (SP). The postural sways were registered by the Static Posturographic System described previously [34, 35]. The experimental protocol consisted of four tests: stance with eyes open (1) and eyes closed (2) on stable support, and with eyes open (3) and eyes closed (4) on foam support. The duration of each measurement was 30 s and the pause between conditions was 2 min.
- Otoscopy, tympanometry and pure tone audiometry.

Video head impulse test

The video head impulse test (vHIT) for the investigation of the vestibulo-ocular reflex (VOR) was carried out using an eHIT USB (BioMed Jena GmbH Biomedizinische Technik, Germany). The equipment included a portable anti-slippage mask, built-in infrared cameras for recording the eye movement and gyroscopes for simultaneous head movement recording. The subjects wearing spectacles were examined 20 min after removing them. The participants in the investigation were seated facing a wall at a distance of 1.5 m, on which markers with a diameter of 5 cm were placed at 1 m above floor level. First, a calibration was performed in which the participants were instructed to look at the marker indicated by the examiner without moving their heads. During the tests, the examiner stood behind the participant, and gave brief, abrupt, horizontal and diagonal patient's head rotations at a small angle (about 10°–20°) to the left and to the right. The impulses were delivered in a way which the patients could not predict. Ten to twenty impulses at a speed above 150º/s were applied for each semicircular canal, and after each rotation the head was maintained in the final position, before returning to the initial position. This technique attempts to limit the masking of overt saccades in the video tracings. During the maneuvres, the patients were instructed to avoid blinking as much as possible, and to keep their gaze firmly fixed on the marker in front of them. The parameters of the VOR gain (the ratio between peak eye velocity and peak head velocity) and the appearance of saccades during or after head impulses to the right and left were applied to evaluate the VOR in response to head movements. The perfect value of gain was accepted to be 1. Normal values of gain were adopted as provided by the manufacturer's parameters—between 0.8 and 1.2. We accepted the following criteria for semicircular canal hypofunction: gain values below 0.8 and/or the presence of covert/overt saccades [16, 36–38].

Vestibular-evoked myogenic potentials (VEMP) tests

The cervical and ocular VEMP tests were performed using a Nihon-Kohden-evoked potentials response unit (Neuropack M1 MEB-9200, Japan). The surface EMG activity was recorded with electrically isolated surface Ag/AgCl electrodes. Air-conducted tone-burst sound stimuli were delivered through headphones with an intensity of 115 dB sound pressure level (SPL) at a frequency of 500 Hz. The duration of the stimuli was 4 ms for cVEMP and 6 ms for

oVEMP, and the presentation rate was 5 Hz. The analysis window was 100 ms wide and the pre-stimulus epoch was 10 ms. The EMG activity before the stimulus and the VEMP response to audio stimulation were measured, and the average of the VEMPs and pre-stimulus EMG activity for 100 stimuli was calculated. The latencies and peak-to-peak amplitudes of these waves were calculated and recorded. The amplitude asymmetry ratio (AR) between a subject's ears was calculated according to the formula:

$$\mathrm{AR}\% = |(\text{Ampl. Left} - \text{Ampl. Right})/ (\text{Ampl. Left} + \text{Ampl. Right})| \times 100. \quad (1)$$

The tests were repeated three times on each subject and the data were averaged to ensure reliability and reproducibility of responses, with a 3-min rest period between the tests.

Cervical VEMP (cVEMP) test protocol

The participants were placed in a semirecumbent position and were asked to rotate their heads away from the stimulated side so as to provide tonic sternocleidomastoid (SCM) muscle activity.

For the registration of cVEMP, the surface electrodes were placed on the middle third of the SCM, with the reference electrode on the upper third of the sternum, and the ground electrode in the middle of the forehead. The EMG signal was amplified (200 μV) and band-pass filtered (5Hz–2000 Hz). The latencies of the first positive peak (p1) and first negative peak (n1), the peak-to-peak amplitude p1–n1, and the amplitude of tonic SCM muscle activity from the pre-stimulus period were measured for each subject. Due to the fact that there is a strong relationship between the tonic EMG activity and peak-to-peak cVEMP amplitude which leads to intra-individual differences, we performed an amplitude normalization by dividing the cVEMP amplitude with the SCM muscle activity from the pre-stimulus period (relative amplitude), thus calculating the interamplitude asymmetry [39]. We had determined that the mean plus two standard deviation was the maximum value allowed as asymmetry [40–43].

Ocular VEMP (oVEMPs) test protocol

All subjects were asked to move to a sitting position and were instructed to look superomedially, at a visual angle of approximately 30°, which had been found to elicit the largest responses compared with other eye positions [40]. The active electrodes were placed approximately 1 cm below the centre of the lower eyelid, contralateral to the stimulated ear. The reference electrode was placed about 1 cm below the active electrode, and the ground electrode was placed on the forehead. The EMG signal was amplified (100 μV) and band-pass filtered (1–1000 Hz). We analyzed the latencies of the first negative peak (n1), first positive peak (p1), peak-to-peak amplitude n1–p1, and the amplitude asymmetry.

Statistical analysis

Data are presented as mean ± standard deviation (SD). All data were explored for normal distribution by the Shapiro–Wilk's W test, $p > 0.05$ for determining the appropriate statistical analysis. Student's t test and paired t test were used for normally distributed data. The non-parametric statistical methods were used when the distribution of variable is not normal (Mann–Whitney U tests and Kruskal–Wallis ANOVA, Spearman's rank correlations). The level of significance was $p < 0.05$. The statistical analyses were performed with Statistica 7.0 (Stat Soft Inc., USA, 2004).

Results

Three groups of participants were involved in the present study: PD patients with agoraphobia, PD patients without agoraphobia, and a control group of healthy subjects. There were no significant differences regarding age and sex distribution between the groups.

Spontaneous nystagmus, head shaking-induced nystagmus, hyperventilation-induced nystagmus and vibration-induced nystagmus were not detected in the three groups. Positional nystagmus was recorded in 8% of the healthy controls, 11% in patients with PD without agoraphobia, and 14% in patients with PD and agoraphobia. In all studied subjects, the slow-phase velocity of registered positional nystagmus was below 5°/s and was not considered pathological. The saccadic test and the slow pursuit eye movement test did not show any abnormalities in the three groups.

All investigated subjects showed normal visual suppression and normal visual enhancement of the horizontal VOR.

Tympanometry was normal in all subjects in the study. Sensorineural hearing loss was identified in 12% of healthy controls, 10% of patients with PD without agoraphobia, and 15% of PD with agoraphobia.

The similarity and lack of statistical differences in clinical neurological symptoms as well as the parameters of VEMPs tests of PD patients with and without agoraphobia allow us to present the results for all the PD patients together, and compare them to those of healthy control subjects.

Table 1 shows the basic parameters of VEMPs for all the investigated subjects. According to the test of normality (Shapiro–Wilk's W test, $p > 0.05$), all VEMP parameters data were normally distributed. Any absence of responses for cVEMPs and oVEMPs for both groups (patients and controls) was not observed. The cVEMPs and oVEMPs

Table 1 Mean values and standard deviations of cVEMP and oVEMP parameters for patients with PD compared with those of healthy control group

Parameters	Healthy control ($n=20$)		Patients with PD ($n=48$)	
	Left ear	Right ear	Left ear	Right ear
cVEMP				
Latency p1 (ms)	13.97 ± 1.34	14.24 ± 1.22	14.45 ± 1.51	13.86 ± 1.12
Latency n1 (ms)	23.73 ± 2.39	23.31 ± 1.12	23.38 ± 2.56	23.22 ± 2.18
Relative p1–n1 amplitude	1.63 ± 0.81	1.75 ± 0.67	1.45 ± 0.76	1.59 ± 0.82
Amplitude asymmetry (%)	15.86 ± 3.25		17.12 ± 4.34	
oVEMP				
Latency n1 (ms)	11.58 ± 1.67	11.55 ± 1.11	11.81 ± 2.02	10.82 ± 1.41
Latency p1 (ms)	16.38 ± 1.39	16.28 ± 1.24	16.42 ± 1.76	15.76 ± 1.37
Amplitude (μV)	4.35 ± 1.83	4.57 ± 2.06	4.61 ± 1.51	4.76 ± 1.61
Amplitude asymmetry (%)	13.67 ± 4.51		14.52 ± 3.87	

Relative amplitude = value of peak-to-peak cVEMP amplitude/value of SCM muscle activity from the prestimulus period

responses were recorded bilaterally for all subjects. There was no significant difference between the VEMPs of both ears for all investigated subjects (paired t test, $p > 0.05$), and between the patients and healthy controls (t test, $p > 0.05$) for mean p1-latency, mean n1-latency and amplitude of cVEMPs and oVEMPs responses (Table 1).

According to the Wang and Young criteria, amplitude asymmetry greater than 35% is considered to be abnormal [44]. In our research, the amplitude asymmetry of VEMPs of PD patients was within normal limits (17% for cVEMPs and 15% for oVEMPs).

The results of vHIT test for one of the patients with PD and agoraphobia are presented in Fig. 1.

Statistical differences of VOR gains values between left and right ears of all investigated subjects (PD patients and healthy controls) for three semicircular canals were not found (Wilcoxon test, $p > 0.05$) as well as between the VOR gains of patients with and without agoraphobia also (Mann–Whitney U test, $p > 0.05$). This gives us a reason to analyze together the data from both ears for all investigated groups.

The distribution of patients with PD and healthy control subjects according to their VOR gains is presented in Table 2.

A VOR gain within normal limits (0.8–1.2) was observed in 67% of the PD patients. A VOR gain above normal limits was not registered in healthy subjects, whereas higher gains were observed in 27% of patients, bilaterally in the three semicircular canals, and in 6%—unilaterally in one of the semicircular canals. None of the tests revealed the presence of overt and covert saccades (Table 2).

Kruskal–Wallis ANOVA by ranks showed an insignificant effect of the "Group" factor for the three semicircular canals ($H(2,115) = 33.24$, $p < 0.001$ for the anterior canal, $H(2,115) = 32.53$, $p < 0.001$ for the lateral canal and $H(2,115) = 31.86$, $p < 0.001$ for the posterior canal). The shift to higher values of VOR gains in both patient groups than that of healthy control was found (Table 3). Compared to healthy controls, the range of values of VOR gains of both patients groups were shifting to higher values, but the differences between VOR gains of the patients and controls were not statistically significant (Table 3).

On the other hand, both the patient groups showed a significantly higher postural instability than healthy controls during quiet upright stance when acute sensory conflict existed (Fig. 2). Significant differences of the length of displacements of COP between patients and controls were observed only during stance on foam pad with eyes closed (Mann–Whitney U test, $p < 0.05$). No significant difference of mean values of the length of displacements of COP was found between the two patient groups and between the patient groups and healthy controls during stance with open and closed eyes on stable support and with open eyes on a foam pad (Mann–Whitney U test, $p > 0.05$). No difference was observed between patients with and without agoraphobia during stance on both supports (stable and foam) (Fig. 2).

There are strong correlations between the mean displacements of COP during stance on foam pad with closed eyes and mean VOR gains for three semicircular canals. Spearman's correlation coefficients were as follows: anterior canal − 0.67, lateral canal − 0.69 and posterior canal − 0.67.

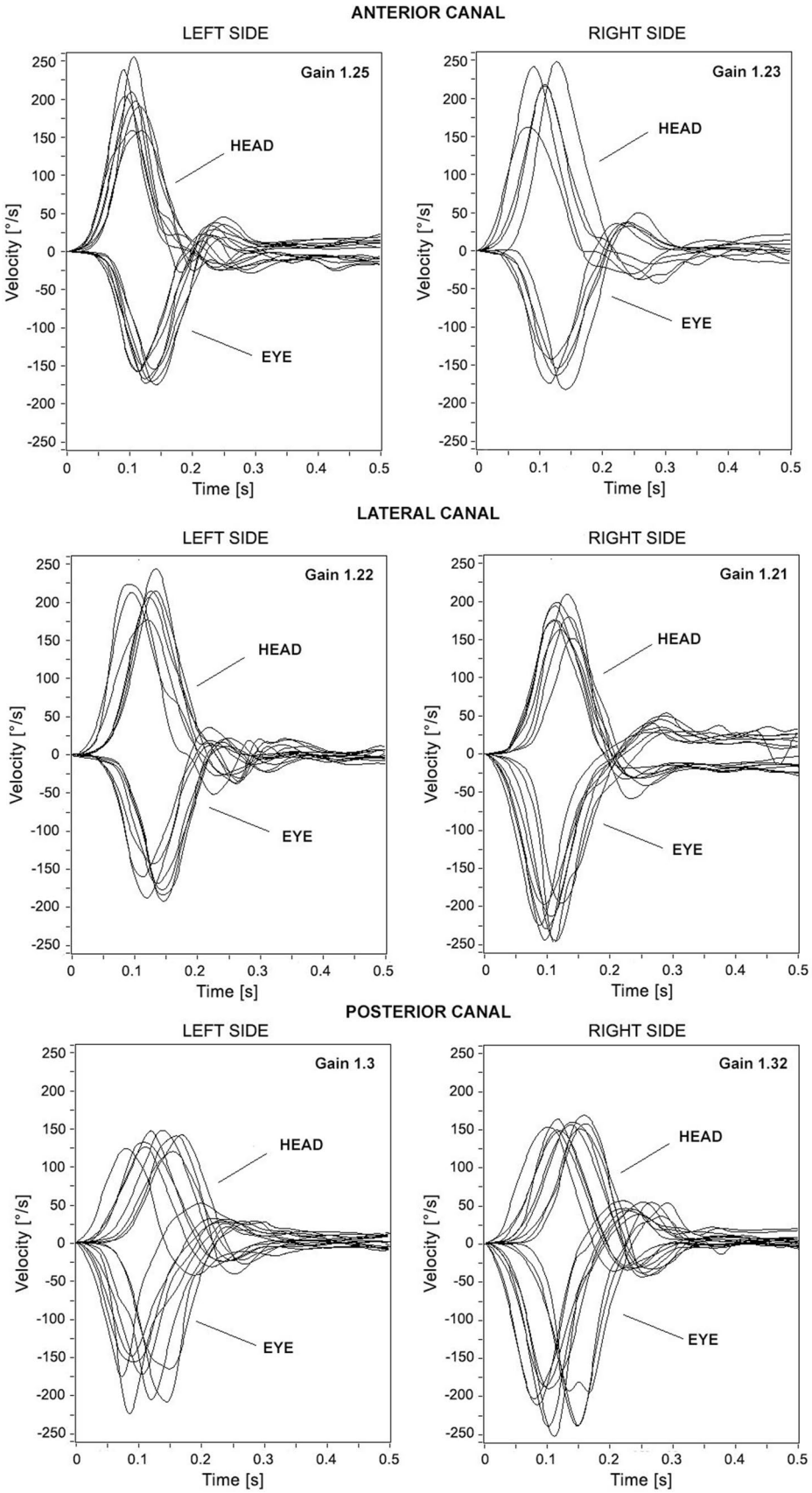

Fig. 1 Raw data of vHIT test in a patient with PD and agoraphobia with high gains in three semicircular canals (lateral, anterior and posterior) and both ears

Table 2 The distribution of patients with PD and healthy controls according to their VOR gains

Finding	PD + A (%)	PD − A (%)	All patients (%)	Healthy controls (%)
Normal	14 (29%)	17 (35%)	31 (64%)	17 (85%)
High VOR gain in all canals	5 (10%)	8 (17%)	13 (27%)	0
Anterior canal high VOR gain	0	0	0	0
Lateral canal high VOR gain	1 (2%)	1 (2%)	2 (4%)	1 (5%)
Posterior canal high VOR gain	0	1 (2%)	1 (2%)	0
Lateral and anterior canals high VOR gain	0	0	0	0
Lateral and posterior canals high VOR gain	1 (2%)	0	1 (2%)	0
Low VOR gain in all canals	0	0	0	0
Anterior canal low VOR gain	0	0	0	0
Lateral canal low VOR gain	0	0	0	0
Posterior canal low VOR gain	0	0	0	2 (10%)
Covert/overt/ multiple saccades	0	0	0	0

VOR vestibulo-ocular reflex, *PD + A* panic disorder with agoraphobia, *PD − A* panic disorder without agoraphobia

Table 3 VOR gains for three semicircular canals of the patients and healthy controls presented by mean value ± SD, median and range

	PD + A	PD − A	Healthy
Anterior canal			
Mean (SD)	1.21 ± 0.07	1.23 ± 0.08	1.08 ± 0.08
Median	1.23	1.24	1.11
Range	0.93–1.28	0.96–1.3	0.82–1.18
Lateral canal			
Mean (SD)	1.23 ± 0.06	1.25 ± 0.07	1.1 ± 0.05
Median	1.25	1.24	1.12
Range	0.92–1.32	0.94–1.31	0.86–1.16
Posterior canal			
Mean (SD)	1.22 ± 0.08	1.22 ± 0.09	1.08 ± 0.06
Median	1.24	1.23	1.1
Range	0.9–1.31	0.9–1.32	0.83–1.13

VOR vestibulo-ocular reflex, *PD + A* panic disorder with agoraphobia, *PD − A* panic disorder without agoraphobia

Discussion

A lot of studies on the vestibular function in patients with PD investigate the VOR of the horizontal semicircular canal [7, 9] and the vestibulo-spinal reflexes [8, 45].

The only research on the otolith function (utricular only) in patients with PD was conducted by Furman et al. [13]. The researchers presumed that there might be a possible otolithic abnormality, based on the fact that some situations (such as "looking up", "closing eyes in the shower", and "leaning far back in a chair") elicit space and motion discomfort (SMD) in panic disorder patients. They performed an analysis of VOR, including otolith-ocular reflex and semicircular canal–otolith (static and dynamic) interaction, using a constant velocity and sinusoidal off-vertical axis rotation (OVAR). The investigators found a higher gain during sinusoidal OVAR in patients, shorter time constants of post-rotatory nystagmus in patients, and a larger modulation of per-rotatory otolith-ocular reflex (which reflects direct otolith-ocular reflex) in anxious patients without height phobia, than in height phobics and controls. The authors make no firm conclusion as to whether those results point to the presence of otolith dysfunction.

We tested the otolith function using two methods which had become well established in the last years: cVEMP and oVEMP. No statistically significant difference was found between PD patients and healthy individuals regarding the latencies of the potentials and the interamplitude asymmetry. This fact gives us sufficient reason to assume that the otolith system (utricular and saccular) is not impaired.

In the present study, we did not find a peripheral vestibular hypofunction (defined as gain ≤ 0.80 and/or presence of covert and overt saccades) in PD patients using vHIT for testing high-frequency VOR of each semicircular canal. This finding is contrary to the investigations where the VOR was tested within the low-frequency range by rotation test or/and unilateral function testing of the horizontal semicircular canal by caloric test, in which a vestibular dysfunction was observed [5, 7, 13]. Our results do not discard the presence of a peripheral vestibular hypofunction, since it is known that the caloric test can be abnormal in certain patients with normal vHIT [43, 46, 47].

An interesting finding in our research is the similarity of vHIT gains of PD patients with and without agoraphobia, and an increase of VOR gain in 34% of all patients with PD.

An increase of VOR gain in PD patients has also been established by other researchers during a whole body rotation test [10, 12]. Moreover, there is evidence that anxiety,

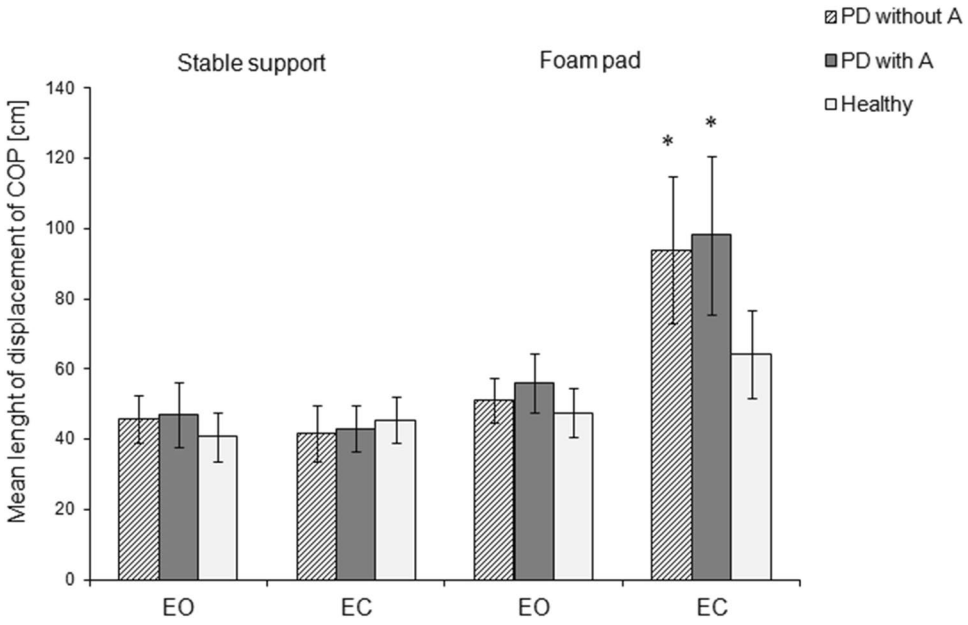

Fig. 2 Changes of postural stability during stance in four experimental conditions, evaluated by mean displacements of the trajectory of COP. *EO* open eyes condition, *EC* closed eyes condition, *PD* patients with panic disorder without agoraphobia and *PD* + *A* patients with panic disorder with agoraphobia. The data are presented by means ± SD. Significant differences between patients groups and healthy control (Mann–Whitney *U* test, $p < 0.05$) are noted by asterisk

arousal and mental stress possess a modulating effect on the VOR [48]. An increased VOR gain was measured through vHIT test in healthy young adults when they were exposed to an increased postural threat [49]. Changes in postural control were found in normal individuals when standing at a height where a stiffer stance with low-amplitude, high-frequency sway was observed [50]. In our previous study on postural stability of PD patients, we found the importance of the visual information on maintenance of postural stability for patients with PD compared to healthy subjects, especially when a sensory conflict exists [51].

In this research, we established the relationship between higher VOR gains and the increase of postural instability when a sensory conflict exist (standing on foam pad with eyes closed). This finding gives us reason to assume that the difficulty of maintaining the equilibrium during stance on foam pad with eyes closed, as well as the head movements during the vHIT test provoke an anxiety from occurrence of negative symptoms of disease and the reaction is hyperactivity of the vestibular system and high instability.

It is known that, in some central vestibular disorders such as migraine and vestibulo-cerebral lesions, the VOR gain is abnormally large [52, 53]. Due to that reason, we have excluded from this investigation patients suffering from migraine and those with previous positive history of vestibular disorders. Additionally, the applied neurotological test battery did not show central vestibular dysfunction in all subjects included in the study. Our results show a lack of abnormality of the vestibular organs in PD patients. We assume that some patients with PD functionally have a low sensitivity threshold of the vestibular system. For those patients, an increase of anxiety level leads to hyperfunction of the vestibular system and an elevation of VOR gains in three semicircular canals. We suggest that the increase of VOR gain may be due to biochemical changes in the brain which take place during anxiety and panic attacks. The neuroanatomical studies showed a strong excitatory input from neural regions involved in processing emotional and affective responses to the vestibular nuclei in the brainstem. The parabrachial nucleus, which processes convergent vestibular, somatic, and visceral information to mediate avoidance conditioning, anxiety and conditioned fear responses, projects to the medial, inferior and superior vestibular nuclei. The vestibular nuclei also receive noradrenergic projections from the locus coeruleus via the coeruleo-vestibular pathway [54, 55]. The norepinephrine elicits an excitatory response on neurons in the inferior vestibular nucleus—the largest nucleus in the vestibular nuclear complex, via activation of α1, α2 and β2-adrenergic receptors [56]. The vestibular nuclear complex also receives a serotoninergic projection from the dorsal raphe nucleus and the nucleus raphe obscurus [54, 55]. It has been shown that histamine participates in the modulation of brainstem vestibular nuclei-related reflexes and functions by excitation of inferior vestibular nucleus neurons via postsynaptic H1 and H2 receptors [57]. We hypothesized that these neural relationships could explain the increased VOR gain in patients with panic disorder. We believe that the vestibular dysfunction in patients with panic disorder is caused by abnormal central modulation of afferent signals coming from peripheral vestibular receptors.

Our research has certain limitations. We have only used two methods for testing the function of the vestibular labyrinth: vHIT and VEMPs. To compare the results between these two methods and the traditional ones, an objective of our future examinations will be the inclusion of the full neurotological battery of tests. Another limitation is the

involvement of patients suffering only from panic disorder; it would be interesting to study the findings from these investigations in patients with other anxiety and depressive disorders. Investigating the effect of therapy of these conditions on test results is a future objective of our work.

Conclusion

The VEMPs and vHIT tests demonstrated that there is no evidence for hypofunction of the semicircular canals in the high-frequency spectrum of VOR functioning and impairment of the otolith system in patients with panic disorder, regardless of their subjective vestibular sensations. The vestibular dysfunction of PD patients might be due to abnormal central modulation of afferent signals coming from peripheral vestibular receptors. The findings of the current study confirm the proposed link between anxiety, panic symptoms and postural instability in PD patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest and report that this is an original paper that has not been submitted elsewhere.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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