Auditory and vestibular dysfunction in patients with Parkinson's disease

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Background
Motor dysfunction in patients with Parkinson disease (PD) is just the tip of the iceberg. Auditory and vestibular dysfunction in patients with PD gained much attention owing to them being one of the nonmotor symptoms.
Aim
To explore abnormalities of pure tone audiometry (PTA), brainstem auditory evoked potentials (BAEPs), vestibular evoked myogenic potential (VEMP), and videonystagmography (VNG) in patients with PD and their correlation with motor and cognitive dysfunction.
Patients and methods
The study was conducted on 20 patients with PD and 15 controls. Selected patients were subjected to evaluation of motor symptoms using Unified Parkinson's Disease Rating Scale (UPDRS) and cognitive function using Parkinson disease-Cognitive Rating Scale (PD-CRS). PTA, BAEPs, cervical VEMPs, and VNG were carried out for all patients and controls.
Results
Patients with PD show higher mean hearing thresholds at all PTA frequencies in both ears than controls. Analysis of BAEP demonstrated that patients with PD have significantly prolonged absolute latencies of wave III and wave V and interpeak latencies of I–III and I–V in both ears than controls. VEMP findings revealed that patients have significantly delayed P13 and N23 latencies and smaller P13–N23 amplitude in both ears than controls. VNG findings showed canal paresis in 60% of patients with PD and nystagmus in 60% of patients with PD. Correlative results revealed statistically significant correlations between VEMP parameters and UPDRS as well as PD-CRS, but there were no statistically significant correlations between PTA frequencies or BAEP latencies and UPDRS or PD-CRS.
Conclusion
Auditory and vestibular dysfunction is common in PD but cannot be totally correlated with the motor and cognitive symptoms.

Keywords:
brainstem auditory evoked potentials, Parkinson, Parkinson disease-Cognitive Rating Scale, pure tone audiometry, Unified Parkinson's Disease Rating Scale, vestibular evoked myogenic potentials, videonystagmography

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Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder of central nervous system that mainly affects the motor system. It occurs owing to loss of dopaminergic neurons not only in the substantia nigra but also in other dopaminergic and nondopaminergic areas of the brain [1,2]. The four major motor symptoms of PD are rigidity, tremor, bradykinesia, and postural instability [3]. Unilateral affection and persisting asymmetry of the cardinal motor features are a diagnostic key in PD, differentiating it from parkinsonian disorders [4].

Furthermore, patients with PD have a multiple of nonmotor symptoms (NMSs), which have a bad effect on their quality of life. The NMSs consist of neuropsychiatric abnormalities, sensory symptoms, autonomic disturbance, sleep disorders, and gastrointestinal problems [5]. Those NMSs are accompanied by dopaminergic and nondopaminergic disorders, including serotoninergic, noradrenergic, and cholinergic systems [6,7].

Lewy bodies and Lewy neurites consisting of α-synuclein are the pathological imprints of PD [8,9]. α-Synuclein pathology has appeared in brain hemispheres, brain stem, spinal cord, and peripheral nervous system [10]. Seidel *et al.* [7] demonstrated the widespread presence of Lewy bodies and Lewy neurites

in brainstem nuclei and fiber tracts including vestibular nuclei. Therefore, diagnostic tools exploring disruption of lower brainstem nuclei, such as vestibular evoked myogenic potentials (VEMP) and brainstem auditory evoked potential (BAEP), are needed for early diagnosis of PD [11]. Previous studies investigated impaired BAEP and VEMP results in patients with PD compared with controls, which were attributed to underlying brainstem dysfunction [12,13].

Hearing affection is a nonmotor manifestation in PD. The natural aging process together with neurodegenerative changes occurring in PD might hinder cochlear transduction mechanisms, thus anticipating presbycusis. α-Synuclein is present predominately in the efferent neuronal system within the inner ear, and it could affect susceptibility to noise-induced hearing loss or presbycusis as explained by Vitale *et al.* [14]. Furthermore, Lai *et al.* [15] stated that as dopamine is a useful neurotransmitter that provides protection of the cochlea from noise exposure, its deficiency in PD can lead to damage to the cochlea and result in hearing loss.

The involvement of the central auditory systems in patients with PD was also confirmed by brain perfusion SPECT and functional MRI. These imaging showed basal ganglia affection on auditory stimulation. Outputs from basal ganglia were found to be directed to the inferior colliculus, medial geniculate nucleus, and temporal cortex [16,17].

PD is associated also with several oculomotor deficits. These include decreased ability in generating volitional saccades and in suppressing visually guided saccades, with generation of visually guided saccades less affected [18,19]. Early studies also suggest reduced responses in optokinetic nystagmus and smooth pursuit gains [20,21], whereas more recent studies suggest no differences to control volunteers [22].

Aim

The aim of this study was to explore the abnormalities of pure tone audiometry (PTA), BAEPs, VEMPs, and videonystagmography (VNG) in patients with PD and their correlation with the motor and cognitive dysfunction in PD.

Patients and methods

Study design and population

This is a case–control study carried out on 20 patients diagnosed as having idiopathic PD and 15 normal controls matched for age and sex. They were recruited in the period between October 2016 and August 2017 from the Neurology Outpatient Clinic, Beni Suef University Hospital. The study was approved by the ethical committee of the neurology department.

Inclusion criteria

Twenty patients fulfilled the criteria for diagnosis of idiopathic PD based on British Brain Bank criteria [23]. Selected patients had the ability to read, write, and do simple calculations.

Exclusion criteria

Patients with major language disturbance; patients with severe physical, auditory, or visual impairment affecting their ability to complete testing; patients with secondary or atypical parkinsonism; patients with evidence of concomitant cerebrovascular stroke temporally related to the onset of the disease; patients with concomitant medical and metabolic illnesses or major psychiatric disorder known to affect cognition; patients with MRI brain showing structural lesion; patients with improper neck movements that interfere with audiological assessment; patients with middle ear diseases, ear infection, ear trauma, or acoustic trauma; or patients using ototoxic drugs were excluded.

Methods

Neurological assessment

The motor function of patients with PD was assessed using Unified Parkinson's Disease Rating Scale (UPDRS). It is made up of the following sections: part I: evaluation of mentation, behavior, and mood; part II: self-evaluation of the activities of daily life; part III: motor evaluation; part IV: complication of therapy; and part V: other complications [24]. The cognitive function of the patients with PD was assessed using Parkinson's Disease – Cognitive Rating Scale (PD-CRS) that covers the full spectrum of cognitive deficits associated with PD, including attention, episodic memory (immediate and delayed recall), naming, visuospatial abilities (visuoconstructional and visuoperceptual abilities), and executive function (working memory, action verbal fluency, and alternating verbal fluency) [25].

Audiological assessment

All subjects who participated in this study were subjected to the following: (a) tonal audiometry in the frequency range of 0.25–8 kHz using clinical audiometer (model Obiter 922, Otometrics; Madsen, Denmark), speech audiometry including speech reception threshold using Arabic spondee words

[26], and word discrimination score, using Arabic phonetically balanced words [27]. The middle ear function was assessed by the acoustic immittance meter Grason-Stadler (GSI 33; Minnesota, Eden Prairie, USA), calibrated according to the ISO standard. (b) BAEPs were obtained using Interacoustics (Eclipse 'EP15'; Denmark). The active electrode is placed on the scalp at the vertex (Fz position of the 10–20 International System of EEG electrode placement), the reference electrodes were placed on the right (A2) and left (Al) mastoids, and the ground electrode is placed on the lower mid-frontal area (Fpz position). Click is presented through TDH39 headphones. Click was presented at a rate of 21.1 stimuli per second in rarefaction polarity at intensity of 80 dB HL. Averaged potentials to 1200 clicks were obtained. Two recordings were obtained to ensure the replicability of the waveforms. The absolute latencies of waves I, III, and V and the interpeak latencies (IPLs) of I–V, I–III, and III–V were analyzed. (c) Cervical vestibular evoked myogenic potential (cVEMP) was performed using Interacoustic Eclipse 'EP15'. The active (positive) electrode, right and then left, is placed on both upper 2/3 of sternocleidomastoid muscles; the inverting (negative) electrode is placed on the upper sternum (suprasternal notch); and the ground electrode is placed on the forehead. Two repeatable recordings were obtained for each condition. During recording, the subject is instructed to raise his head and tilt it away from the stimulated side throughout the test to have good muscle tone. cVEMP responses were obtained by binaural acoustic stimulation and recorded from bilateral sternocleidomastoid muscles. Short tone burst at frequency of 500 Hz of a rarefaction polarity. Intensity used is 95 dB HL presented through TDH39 headphones. The latencies of peaks P13 and N23 (ms), P13–N23 peak-to-peak amplitude (μV), and inter-aural amplitude difference (IAAD) ratio were measured [28]. (d) Videonystagmography (VNG) ICS Chart EP 200, Otometrics (Denmark), which composed of (I) normal eye movement functions testing using standardized test battery (smooth pursuit testing, Saccade testing, spontaneous nystagmus testing, and eccentric gaze testing); (II) positional and positioning testing; and (III) water caloric tests: bithermal caloric tests were performed, where each ear was irrigated with water at temperatures of 30 and 44°C for 40 s. Canal paresis and directional preponderance were calculated according to Jongkees' formula [29]. Values more than 20% for canal paresis and 25% for directional preponderance were considered abnormal.

Statistical methods

The data were coded and entered using the statistical package for the social sciences (SPSS version 15). Student *t*-test was used for comparison between means of two groups of quantitative variables. χ^2-Test was used for comparison between two groups of categorical data or frequency of events. The Pearson correlation coefficient (*r*) was used to describe the degree of relationship between two variables. The sign of correlation coefficient (+, −) defines the direction of the relationship, either positive or negative. The *P* value of at least 0.05 is not statistically significant and less than 0.05 is statistically significant.

Results

This is a case–control study conducted on 20 patients diagnosed as having PD and 15 normal healthy controls. The mean age of patients with PD was 64.80±7.488 years, whereas the mean age of controls was 64.27±5.257 years. Overall, 80% (*n*=16) of the included patients with PD were males and 20% (*n*=4) were females. Regarding controls, 53.33% (*n*=8) were males and 46.67% (*n*=7) were females. There was no statistically significant difference between the patients and control groups in either age (*P*=0.815) or sex (*P*=0.0926).

The motor function of patients with PD was assessed using UPDRS. The mean value of the total score of UPDRS for patients with PD was 32.65±14.662. The cognitive function of patients with PD was assessed using PD-CRS. The mean value of the total score of PD-CRS for patients with PD was 66.95±15.477.

Regarding PTA, patients with PD were found to have significantly higher mean hearing threshold values in both ears than controls in 250, 500, 1000, 2000, 4000, and 8000 Hz (Table 1).

Regarding BAEP wave latencies, two (10%) patients with PD were found to have absent BAEP waves on both sides. Comparison between patients with PD having preserved BAEP waves and controls revealed that patients with PD had significantly prolonged absolute latencies of wave III and wave V, as well as I–III and I–V interpeak latencies on right side than controls, but there was no statistically significant difference between patients and controls in wave I latency and III–V interpeak latency. Regarding the left side, patients with PD were found to have significantly prolonged absolute latencies of wave III and wave V, as well as interpeak latencies of I–III, I–V,

Table 1 Comparison of the mean hearing thresholds in patients with Parkinson disease and controls regarding pure tone average (dB HL) in the right and left ears

Pure tone average	Patients (*n*=20) [mean (SD)]	Controls (*n*=15) [mean (SD)]	*P* value
Right pure tone average (Hz)			
250	23.50 (3.285)	15.67 (4.952)	0.000*
500	23.75 (2.221)	17.33 (3.2)	0.000*
1000	23.50 (3.285)	2.221 (2.582)	0.000*
2000	26.75 (7.482)	20.00 (4.226)	0.004*
4000	41.75 (11.840)	19.67 (4.419)	0.000*
8000	54.25 (14.075)	18.67 (2.968)	0.000*
Left pure tone average (Hz)			
250	24.00 (4.168)	17.00 (3.162)	0.000*
500	22.75 (3.024)	17.67 (3.716)	0.000*
1000	24.25 (3.354)	17.67 (3.200)	0.000*
2000	26.50 (5.871)	17.67 (4.169)	0.000*
4000	44.00 (10.588)	18.00 (3.162)	0.000*
8000	56.50 (10.894)	21.33 (2.968)	0.000*

$P \geq 0.05$, NS. *$P < 0.05$, significant.

Table 2 Brainstem evoked potential results in Parkinson disease group and control group

	Patients (*n*=18) [mean (SD)]	Controls (*n*=15) [mean (SD)]	*P* value
Right brainstem auditory evoked potential			
I latency	1.38 (0.14)	1.39 (0.15)	0.877
III latency	3.79 (0.18)	3.47 (0.27)	0.000*
V latency	5.87 (0.2)	5.47 (0.19)	0.000*
I–III latency	2.41 (0.23)	2.07 (0.23)	0.000*
I–V latency	4.48 (0.24)	4.08 (0.21)	0.000*
III–V latency	2.08 (0.15)	2.001 (0.26)	0.308
Left brainstem auditory evoked potential			
I latency	1.38 (0.16)	1.37 (0.2)	0.919
III latency	3.74 (0.17)	3.51 (0.2)	0.001*
V latency	5.86 (0.14)	5.34 (0.16)	0.000*
I–III latency	2.36 (0.26)	2.14 (0.25)	0.017*
I–V latency	4.44 (0.25)	3.97 (0.21)	0.000*
III–V latency	2.12 (0.11)	1.83 (0.2)	0.000*

$P \geq 0.05$, NS. *$P < 0.05$, significant.

Table 3 Cervical vestibular evoked myogenic potential results in Parkinson disease group and control group

	Patients (*n*=18) [mean (SD)]	Controls (*n*=15) [mean (SD)]	*P* value
Right vestibular evoked myogenic potential			
P13 latency	17.288 (1.63)	13.7 (1.01)	0.000*
N23 latency	25.59 (2.17)	22.4 (1.07)	0.000*
Amplitude P13–N23	35.91 (14.95)	51.62 (13.30)	0.004*
Left vestibular evoked myogenic potential			
P13 latency	16.98 (1.47)	14.25 (0.99)	0.000*
N23 latency	24.95 (2.5)	22.57 (1.64)	0.006*
Amplitude P13–N23	37.53 (19.36)	67.13 (17.15)	0.000*
IAAD	17.49 (13.71)	19.71 (11.36)	0.663

$P \geq 0.05$, NS. *$P < 0.05$, significant.

and III–V, but there was no statistically significant difference between patients and controls in wave I latency (Table 2).

Regarding VEMP parameters, four (20%) patients with PD were found to have absent VEMP on right side, eight (40%) patients were found to have absent VEMP on left side, and 10 (50%) patients were found to have absent IAAD. Comparison between patients with PD with preserved VEMP and controls revealed that patients with PD had significantly longer P13 latency and N23 latency than controls and significantly smaller P13–N23 amplitude than controls in both right and left side. There was no statistically significant difference between patients and controls in IAAD (Table 3).

Table 4 Videonystagmography findings in patients with Parkinson disease and controls

Videonystagmography	Patients [*N* (%)]	Controls [*N* (%)]	*P* value
Nystagmus			
Absent	8 (40)	15 (100)	0.005*
Present	12 (60)	0	
Saccade			
Normal	16 (80)	15 (100)	0.066
Abnormal	4 (20)	0	
Pursuit			
Normal	17 (85)	15 (100)	0.117
Abnormal	3 (15)	0	
Caloric			
Normal	8 (40)	15 (100)	0.0002*
Canal paresis	12 (60)	0	

$P \geq 0.05$, NS. *$P < 0.05$, significant.

Table 5 Correlation between pure tone average thresholds and Unified Parkinson's Disease Rating Scale and Parkinson disease-Cognitive Rating Scale in patients with Parkinson disease

Pure tone average	Unified Parkinson's Disease Rating Scale		Parkinson disease-Cognitive Rating Scale	
	r Coefficient	*P* value	*r* Coefficient	*P* value
Right pure tone average (Hz)				
250	–0.470	0.036*	0.314	0.177
500	–0.281	0.230	0.297	0.204
1000	–0.372	0.106	–0.012	0.960
2000	–0.016	0.948	0.273	0.243
4000	–0.001	0.997	0.282	0.228
8000	–0.013	0.957	0.122	0.609
Left pure tone average (Hz)				
250	–0.191	0.419	0.166	0.483
500	–0.220	0.350	0.301	0.197
1000	–0.209	0.377	–0.264	0.260
2000	–0.125	0.599	0.154	0.516
4000	0.123	0.605	0.310	0.184
8000	–0.062	0.794	0.325	0.162

r, Pearson's coefficient. $P \geq 0.05$, NS. *$P < 0.05$, significant.

VNG results showed that 12 (60%) of patients with PD had canal paresis, where two (10%) of them had right canal paresis, six (30%) of them had left canal paresis, and four (20%) of them had bilateral canal paresis. Twelve (60%) patients with PD showed spontaneous nystagmus. Four (20%) patients with PD had abnormal saccadic testing and three (15%) had abnormal smooth pursuit (Table 4).

Correlative results revealed no statistically significant correlation between UPDRS and all PTA frequencies on both sides except 250 Hz frequency on the right side. There was also no statistically significant correlation between PD-CRS and all PTA frequencies on both sides (Table 5).

There was no statistically significant correlation between UPDRS and BAEP wave latencies on both sides. There was also no statistically significant correlation between PD-CRS and BAEP wave latencies on both sides except wave I latency on left side (Table 6).

There was a statistically significant positive correlation between UPDRS and P13 latency and N23 latency on both sides, but there was no statistically significant correlation between UPDRS and P13–N23 amplitude on both sides. There was a statistically significant negative correlation between PD-CRS and N23 latency on right side, and there was a statistically significant positive correlation between PD-CRS and P13–N23 amplitude on right side but there was no statistically significant correlation between PD-CRS and P13 latency on right side. There was no statistically significant correlation between PD-CRS and P13 latency, N23 latency, and P13–N23 amplitude on the left side. There was no statistically significant correlation between both UPDRS and PD-CRS and IAAD on both sides (Table 7).

Table 6 Correlation between brainstem auditory evoked potential latencies and Unified Parkinson's Disease Rating Scale and Parkinson disease-Cognitive Rating Scale in patients with Parkinson disease

Brainstem auditory evoked potential	Unified Parkinson's Disease Rating Scale		Parkinson disease-Cognitive Rating Scale	
	r Coefficient	*P* value	*r* Coefficient	*P* value
Right brainstem auditory evoked potential				
I latency	–0.128	0.614	0.103	0.684
III latency	0.352	0.152	–0.319	0.197
V latency	–0.006	0.980	–0.241	0.336
I–III latency	0.342	0.164	–0.305	0.218
I–V latency	0.074	0.771	–0.247	0.324
III–V latency	–0.436	0.070	0.053	0.836
Left brainstem auditory evoked potential				
I latency	0.053	0.833	–0.492	0.038*
III latency	0.049	0.847	0.046	0.856
V latency	0.148	0.557	–0.114	0.653
I–III latency	0.010	0.969	0.342	0.165
I–V latency	0.008	0.975	0.190	0.450
III–V latency	0.089	0.725	–0.231	0.357

r using Pearson's coefficient. $P \geq 0.05$, NS. *$P < 0.05$, significant.

Table 7 Correlation between vestibular evoked myogenic potential parameters and Unified Parkinson's Disease Rating Scale and Parkinson disease-Cognitive Rating Scale in patients with Parkinson disease

Vestibular evoked myogenic potential	Unified Parkinson's Disease Rating Scale		Parkinson disease-Cognitive Rating Scale	
	r Coefficient	*P* value	*r* Coefficient	*P* value
Right vestibular evoked myogenic potential				
P13 latency	0.651	0.006*	–0.424	0.102
N23 latency	0.647	0.007*	–0.506	0.046*
Amplitude P13–N23	–0.419	0.107	0.695	0.003*
Left vestibular evoked myogenic potential				
P13 latency	0.664	0.019*	–0.387	0.214
N23 latency	0.580	0.048*	–0.117	0.717
Amplitude P13–N23	–0.306	0.334	0.387	0.214
IAAD	0.373	0.288	–0.149	0.681

r using Pearson's coefficient. $P \geq 0.05$, NS. *$P < 0.05$, significant.

Discussion

This study showed that patients with PD were found to have significantly higher mean hearing threshold values in both ears than controls in 250, 500, 1000, 2000, 4000, and 8000 Hz. Correlative results revealed no statistically significant correlation between UPDRS or PD-CRS and PTA frequencies on both sides.

The results of PTA in patients with PD have varied among different studies. Yýlmaz *et al.* [30] reported that patients with PD showed significant elevations of PTA thresholds in 4000 and 8000 Hz frequencies ($P<0.05$), whereas they did not find statistically significant increases in hearing thresholds of patients with PD in frequencies of 250, 500, 1000, and 2000 Hz. Fradis *et al.* [31] have reported no significant difference in PTA results in 500–8000-Hz frequencies between patients with PD and controls. Additionally, it has been reported that the incidence of PD in a group of patients with hearing loss was 1.77-fold higher than that in the non-hearing-loss group [15].

Regarding BAEP wave latencies in the current study, two (10%) patients with PD were found to have absent BAEP waves on both sides. Comparison between patients with PD with preserved BAEP waves and controls revealed that patients with PD had significantly delayed absolute latencies of wave III and wave V, as well as I–III and I–V interpeak latencies on right side than controls, but there was no statistically significant difference between patients and controls in wave I latency and III–V interpeak latency. Regarding the left side, patients with PD were found to have significantly delayed absolute latencies of wave III and wave V, as well as interpeak latencies of I–III, I–V and III–V, but there was no statistically significant difference between patients and controls in wave I latency.

The results of brainstem auditory response in patients with PD have varied across various studies. Tachibana *et al.* [32] have reported statistically significant increase in V wave peak latency as well as I–V and III–V IPLs for patients with PD, and Gawel *et al.* [33] reported prolongation of V wave latency in patients with PD. On the contrary, Tsuji *et al.* [34], Chiappa [35], and Prasher and Bannister [36] have reported normal BAEPs in patients with PD.

According to the results of Yýlmaz *et al.* [30], there was a statistically significant increase in V wave peak latency and I–V IPLs, but they did not find any significant difference in I and III wave peak latencies or I–III and I–V IPLs for patients with PD. Although they found increase in III–V IPLs of patients with PD, it was not statistically significant.

This study revealed no statistically significant correlation between UPDRS or PD-CRS and BAEP wave latencies on both sides.

Our findings are confirmed by a study conducted by Alexa *et al.* [37] who showed bilateral delay in auditory evoked potential response (ABR) waves II, III, IV, and V and IPL III–V in PD and concluded that the auditory system is involved equally on both sides, regardless of the asymmetry of motor manifestation.

It is possible that the neurodegenerative process in PD affects the functionality of central auditory pathway, leading to a prolongation of wave latencies and peak intervals of auditory evoked potentials [14].

Regarding VEMP parameters in this study, four (20%) patients with PD were found to have absent VEMP on right side, eight (40%) patients were found to have absent VEMP on left side, and 10 (50%) patients were found to have absent IAAD. Comparison between patients with PD with preserved VEMP and controls revealed that patients with PD had significantly longer P13 latency and N23 latency than controls and significantly smaller P13–N23 amplitude than controls in both right and left sides. There was no statistically significant difference between patients and controls in IAAD.

Similar to our findings, Pollak *et al.* [38] demonstrated vestibular involvement in 54 patients with PD; 37% had bilaterally absent cVEMPs elicited with air-conducted stimuli and 7% had unilaterally absent responses; mean latencies were not significantly different between the groups. However, the patient and the control groups were not adequately matched for age (PD group: 66±10 years, control group: 46±15 years, $P<0.001$). Furthermore, Halberstadt and Balaban [39] reported a high statistically significant difference in IAD between the patients with PD and the age-matched control group.

In contrast, Pötter-Nerger *et al.* [13] concluded that cVEMP latencies and amplitudes did not differ significantly between patients with PD and healthy controls at the group level. However, ocular VEMP latencies, especially in bone conducted stimuli at the symptomatic side, were significantly prolonged, but amplitudes did not differ significantly.

This study revealed a statistically significant positive correlation between UPDRS and P13 latency and N23 latency on both sides, but there was no statistically significant correlation between UPDRS and P13–N23 amplitude on both sides. There was a statistically significant negative correlation between PD-CRS and N23 latency on right side, and there was a statistically significant positive correlation between PD-CRS and P13–N23 amplitude on right side, but there was no statistically significant correlation between PD-CRS and P13 latency on the right side and P13 latency, N23 latency, or P13–N23 amplitude on the left side. There was no statistically significant correlation between both UPDRS and PD-CRS and IAAD on both sides.

In two studies led by De Natale *et al.* [40,41] in groups of 33 and 24 patients with PD in total, there was significantly more abnormal individual masseter, ocular, and cVEMPs in comparison with an age-matched control group ($P<0.001$). At the group level, the amplitudes of, in particular, the masseter and ocular VEMPs were significantly smaller in comparison with the healthy control subjects, and the individual results showed a significant correlation with postural instability and rapid eye movement sleep behavior disorder screening scores.

In a recent study led by Venhovens *et al.* [42], abnormal central vestibular function test results were found to be mostly asymptomatic in patients with PD. Patients with PD with falling incidents were found to have significantly more abnormal vestibular test results compared with the nonfalling patients. Apart from well-established causes of falls (freezing of gait, orthostasis, cognitive problems, and postural instability), ~10–18% of the patients have vestibular dysfunction as the only identifiable cause for falling.

On the contrary, the published consensus-based overview concerning the risk factors and

management of falls in PD did not specifically mention vestibular dysfunction as a contributing cause [43].

Interestingly, Hassan and Shalash [44] found that rigidity and bradykinesia in patients with PD related to ABR and cVEMP responses, whereas tremor was not. In addition, the correlations were confined to ABRs and cVEMPs and not ocular vestibular evoked myogenic potential (oVEMP); this might be explained by the midbrain and pontine pathological changes and noninvolvement of vestibulo-ocular pathways in the pathophysiology of those features. Tremor has a different pathophysiology compared with rigidity and bradykinesia and is characterized by involvement of the cerebellothalamocortical circuit in its pathogenesis. This explained the lack of correlation with auditory and vestibular responses [45].

The abnormalities in ABR and VEMP responses reflected dysfunction of different levels of the brain stem and is consistent with caudal–rostral brainstem pathological changes as proposed by Braak *et al.* [46]. So ABR and VEMPs could be potential electrophysiological biomarkers for PD. The asymmetry in brainstem functions is an important factor, particularly when investigating vestibular dysfunction in PD. Whether these audiovestibular deficits are intrinsic to PD or secondary to a more complex impaired processing of sensorial inputs occurring over the course of illness remains to be determined [44].Regarding VNG parameters in our study, 12 (60%) patients with PD were found to have canal paresis, where two (10%) of them had right canal paresis, six (30%) of them had left canal paresis, and four (20%) of them had bilateral canal paresis. Moreover, 12 (60%) patients with PD showed spontaneous nystagmus. In addition, four (20%) patients with PD had abnormal saccadic testing and three (15%) had abnormal smooth pursuit.

Most studies into oculomotor deficits associated with PD have investigated horizontal ocular movements. A small number of studies have investigated vertical saccades and smooth pursuit; however, little is known about the effect of PD on vertical optokinetic nystagmus [47,48].

Bassetto *et al.* [49] led a study on 30 patients with PD and observed the presence of uneven eye motion calibration, semi-spontaneous nystagmus (with eyes opened), asymmetric optokinetic nystagmus, asymmetric peri-rotational nystagmus, asymmetric nystagmus directional preponderance, and unilateral and bilateral labyrinthine hyporeflexia and hyperreflexia. Bilateral labyrinthine hyporeflexia was also noted as a significant finding by Reichert *et al.* [50] and Gushikem [51] in Parkinson's studies with older patients. Dolowitz [52] found hyperreflexia in most analyzed patients.

According to Silveira *et al.* [53], reduced response in caloric tests may occur owing to aging-related alterations in the vestibular system. Various studies make reference to loss of hair cells in the cristae ampullaris and maculae, reduced number of nerve cells in the vestibular ganglion, degenerated otocones, reduced labyrinthine blood flow, progressive neural stability depression, reduced compensatory capacity of ocular-vestibular reflexes (responsible for maintaining stable eyesight during head movements), and vestibular-spinal reflexes (responsible for bodily balance) [54,55].

Further studies are needed to confirm these findings on a larger number of patients and to explore its relation with other features of PD, such as gait, postural abnormalities, and nonmotor symptoms related to brainstem dysfunction.

Conclusion

Auditory and vestibular abnormality can be considered one of the nonmotor symptoms in PD but cannot be totally correlated with the motor and cognitive symptoms in PD. They can be detected by impaired responses in PTA, BAEPs, VEMPs, and VNG. Such abnormality reflected dysfunction of different levels of the brain stem.

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Conflicts of interest

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