Auditory brainstem evoked responses and vestibular evoked myogenic potentials: potential biomarkers in Parkinson's disease

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Objective
The aim of this study was to investigate brainstem functions in Parkinson's disease (PD) through studying auditory brainstem evoked responses (ABRs), and ocular and cervical vestibular evoked myogenic potentials (oVEMP and cVEMP) and to explore their relation with motor symptoms, if any.
Study design
Fifteen individuals diagnosed as having idiopathic PD and 15 age-matched controls were included. The PD patients were evaluated using the Unified Parkinson's Disease Rating Scale, the Hoehn and Yahr Scale, and the Schwab and England Scale. The subscores of major symptom were calculated, such as tremor, rigidity, bradykinesia, and axial signs. During medication 'on' states, PD patients and controls underwent pure-tone audiometry, speech audiometry, tympanometry, ABR, oVEMP, and cVEMP. The test findings in PD patients were grouped into ipsilateral and contralateral results in relation to the clinically more affected motor side and were compared with the age-matched controls.
Results
PD patients showed abnormal ABR wave morphology, prolonged absolute latencies of ABR wave V, and I–V interpeak latencies. Absent responses were the evident abnormality seen in oVEMP. Prolonged latencies with reduced amplitudes were seen in cVEMP responses. The main motor features of PD (rigidity and bradykinesia) were correlated to the ABR and cVEMP responses contralateral to the clinically more affected side.
Conclusion
Dysfunction at different levels of the brainstem was confirmed in patients with PD. The impairment of ABRs and VEMP responses is related to characteristic clinical asymmetry of PD and its cardinal motor features. ABRs and VEMPs could be used as potential electrophysiological biomarkers for PD.

Keywords:
auditory brainstem evoked response, brainstem, motor parkinsonism, vestibular evoked myogenic potential

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Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder caused by degeneration of midbrain dopaminergic neurons of the substantia nigra (SN) producing its main motor cardinal features. The four key motor symptoms that are associated with PD include tremor, rigidity, bradykinesia, and postural abnormalities [1]. Unilateral onset and persisting asymmetry of the cardinal motor features are diagnostic hallmarks of PD, differentiating it from similar but distinct parkinsonian disorders [2]. This clinical asymmetry is associated and related to asymmetrical degeneration of dopaminergic neurons of the SN, striatal dopaminergic receptors, and their cortical connections [3].

Lewy bodies composed of α-synuclein and Lewy neuritis and their distribution are the pathological hallmark of PD [4]. Braak *et al.* [5] proposed that a pathological progression of PD starts caudally from the dorsal motor vagal nucleus in the medulla and then ascends in the brainstem and finally involves the neocortex. Thus, most brainstem nuclei are involved in early stages (I–III) that explains the preclinical and early emergence of nonmotor symptoms, whereas the SN is involved in stage III [6]. Recently, Lambert *et al.* [7] showed brainstem asym- metries in 34 right-handed healthy individuals using new neuroimaging analysis techniques, demonstrating highly significant differences within

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localized regions that corresponded to motor and vocalization networks. To date, there is no published data to explore whether the motor asymmetry in PD is associated with asym- metry in brainstem functions.

Auditory brainstem evoked responses (ABRs) are short-latency potentials recorded from the surface of the head during a brief acoustic stimulation. These potentials, which consist of a series of positive and negative waves recorded within 10^0ms of the stimulus onset, are routinely used in clinical practice to evaluate the function of the auditory nerve and auditory pathways in the brainstem [8].

Vestibular evoked myogenic potentials (VEMPs) provide useful information on brainstem functions, as the neural pathways of both ocular and cervical vestibular evoked myogenic potentials (oVEMP and cVEMP) pass through the brainstem. VEMPs are short-latency manifestations of vestibulo-ocular and vestibulocollic reflexes that originate from the utricle and the saccule. In the central nervous system, the cVEMPs are mediated by the vestibular nuclei, mostly the inferior nucleus and uncrossed medial vestibulospinal tract descending in the lower brainstem and spinal cord [9]. In contrast, the oVEMP neuronal pathway is through the vestibulo-ocular reflex with activation of the vestibular nerve and vestibular nuclear complex traveling up the medial longitudinal fasciculus, where at some point it decussates, ending at the oculomotor nuclei, ocular nerves, and the extraocular muscles [10].

For the purpose of early clinical evaluation and effective patient management, diagnostic strategies for PD might be supplemented for individuals at risk using tests designed to elicit 'soft' PD signs. Accordingly, the objective of this study was to study the brainstem functions in PD through studying ABR and VEMPs and to explore their relation with the motor symptoms, if any. Disruptions within the gain setting nuclei of the brainstem and their symmetry were also highlighted.

Patients and methods

Patients

Study group

Prospective assessment of 15 individuals diagnosed as having idiopathic PD was carried out. Patients were diagnosed as having idiopathic PD according to the British Parkinson's Disease Society Brain Bank criteria [2]. Exclusion criteria included dementia, severe motor disability, improper neck movements, middle ear diseases, and pure-tone audiometric thresholds exceeding 50^0dBHL for frequencies 500–4000^0Hz.

Control group

The control group comprised 15 age-matched normal volunteers serving as controls to provide a reference of auditory and vestibular workup. They had no history of neurological or auditory disorders. Pure-tone audiometric thresholds did not exceed 20^0dBHL for frequencies 500–4000^0Hz.

Informed consent was obtained from all individuals before participation in the present study after explaining the test procedures, benefits, and risks according to the ethical rules.

Procedures

Neurological workup

All participants were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS), the Hoehn and Yahr Scale (H&Y), and the Schwab and England Scale (S&E) in 'medication-off' and 'medication-on' states by a movement disorders expert. These scales objectively rate an individual patient's disability at a particular moment in time. Each scale score is a reflection of disease burden on the individual patient and is useful in describing disease progression and treatment response with time. Different UPDRS subscales were estimated, including the activity of daily living (UPDRS-I), motor (UPDRS-III), UPDRS-IV, and total UPDRS scores. Furthermore, subscores of major symptoms in the medication 'off' state were calculated, such as tremor (items 20 and 21 of UPDRS), rigidity (item 22), bradykinesia (items 18, 19, 23, and 24), and axial signs (items 27, 28, 29, and 30) [11].

Audiovestibular workup

All patients were tested in medication 'on' states to decrease electromyographic muscle artifacts and ensure patients' cooperation. They underwent full history taking for complaints related to the auditory/vestibular system, and audiological evaluation to assess the peripheral auditory system, in the form of pure-tone and speech audiometry, using the two-channel audiometer Grason-Stadler Inc. (Eden Prairie, Minnesota, USA) model 61 calibrated according to ANSI (1969) in a sound-treated room IAC model 1602 (IAC Acoustics, Taastrup, UK). The middle ear functions were tested using the acoustic immittance meter Grason-Stadler Inc. model 33. ABR and VEMP were performed for all participants of the study and control groups using the ICS Charter EP

200 (GN Otometrics, Denmark) evoked potential system.

Auditory brainstem evoked responses

The active electrode was mounted to the middle of the forehead (Fpz), the reference electrode to the ipsilateral mastoid (M1), and the ground to the contralateral one (M2). The test procedures were carried out as described in the protocol of Sininger [12].

Analysis of ABR was carried out quantitatively to assess the absolute latencies of waves I, III, and V (re: stimulus onset) and interpeak latencies I–III, III–V, and I–V. This was carried out both at high stimulus level (90^0dBnHL) and at lower intensities down to thresholds. The interaural latency difference and the latency/rate function were studied at high stimulus intensity. Qualitative analysis for the waveform morphology comprised the subjective judgment on the shape and quality of the waveforms. ABR waveform morphology was considered abnormal when poorly or fairly identifiable (broad or ill-defined peak) and/or repeatable ABR waves (I, III, and V) were detected at maximum intensity (90^0dBHL) [13]. The ABR analysis was performed for each participant in view of his audiogram, to avoid misinterpretation of results.

Vestibular evoked myogenic potentials

Ocular vestibular evoked myogenic potential test

The participant was tested in a sitting position. The active electrode was placed on the inferior oblique muscle 3^0mm inferior and at the center of lower eyelid. The reference electrode was positioned at the chin and one ground electrode was placed on the forehead. The participant was instructed to look upward and maximum upgaze was maintained during oVEMP stimulation and recording. The vertical eye position was at an angle of ~30–35 above horizontal. The test procedures were carried out as described in the protocol of Wang *et al.* [14].

Monaural stimulation with contralateral eye recording was used for recording oVEMPs. The oVEMP response included the initial negative–positive biphasic waveform that comprised peaks nI and pI. Two runs were performed to confirm the reproducibility of peaks nI and pI. Conversely, oVEMPs were termed absent when the biphasic waveform was lacking. The latencies of peaks nI and pI, amplitude nI–pI, and interaural amplitude difference (IAD) ratio were measured. The latter was defined as the difference in the amplitude nI–pI on the right and left ears divided by the sum of amplitude nI–pI of both multiplied by 100 [15].

Cervical vestibular evoked myogenic potentials test

The participant was seated with the head turned sideways toward one shoulder to activate the sternocleidomastoid muscle. The active electrode was placed on symmetrical sites at midpoints of each sternocleidomastoid muscles, with a reference electrode on the suprasternal notch and a ground electrode on the forehead. The test procedures carried out were as described in the protocol of Akin *et al.* [16]. Monaural acoustic stimulation with ipsilateral recording was used for recording cVEMPs. The N13–P13 wave latencies, amplitudes, and IAD were measured. They were classified into normal and abnormal according to the control group normative data.

For analysis purposes, the test findings of ABRs, oVEMPs, and cVEMPs in PD patients were grouped into ipsilateral and contralateral results. This was in relation to the clinically more affected (CMA) motor side – that is, if the CMA of PD was right, then the ipsilateral result was that of the right ear and the contralateral result was that of the left ear. Both the ipsilateral and contralateral test results were compared with the mean values of both sides of the age-matched healthy controls, and then correlated to different UPDRS off scores. The interpretation as abnormal peak latencies, interpeak intervals, and amplitude ratios was considered when values exceeded the 2^0SD from the mean of the control group.

Statistical analysis

Statistical analyses were performed using the IBM computer statistical package for the social sciences (SPSS) program version 18 (SPSS Inc., Chicago, Illinois, USA). Qualitative data were described using number and percent. Quantitative data were described using mean and SD. Association between categorical variables was tested using the $\chi 2$-test. Comparison between two independent variables was made using the independent *t*-test. Correlations between quantitative variables were assessed using Spearman's coefficient. The level of statistical significance (*P* value) was set at 0.05 and 0.01. A statistician was used for guidance in the study.

Ethics

The Research Ethics Committee approved the study.

Results

Fifteen patients with idiopathic PD (12 male and three female) participated in the current study. Their ages

ranged from 35 to 76 years (mean ± SD: 59.20 ± 10.08 years). The duration of disease was 5.50 ± 2.96 years (range: 2–10 years) and the mean age of onset was 53.77 ± 11.49 years. The control group comprised 10 men and five women, with a mean age of 59 ± 9 years (range: 37–70 years). No statistically significant difference existed between the two study groups as regards age ($t = 0.002$, $P = 0.9$) or sex.

Neurologically

The mean total UPDRS and mean disease disability (the S&E) scores were 41.33 ± 30.20 and 68.67 ± 22.30, respectively. Patients were of variable disease stages ranged from stage II to V of H&Y Scale off with mean 2.73 ± 0.84 reflecting moderate degree of disability. The motor (UPDRS-III) scale showed that the CMA side was on the right side in seven patients and on the left side in the remaining eight patients. The motor characters of PD patients are presented in Table 1.

Audiological evaluation

The PD patients had poorer Pure tone average (PTA) thresholds mainly in the high frequencies 4 and 8 kHz bilaterally compared with the age-matched control group. This difference was statistically significant (Table 2). In total, seven PD patients had sensorineural hearing loss of mild-to-moderate degree (bilateral symmetrical in five and unilateral in two). This degree did not hinder the application of the electrophysiological test battery. The PD patients showed excellent mean word recognition score %. The middle ear pressure was normal as shown from type A tympanograms in all study group participants. The acoustic reflex was elicited normally in all controls and in the majority of PD patients. Abnormal acoustic reflex thresholds whether absent or elevated were seen in seven ears (three ipsilateral to CMA side and five contralateral to CMA side).

Electrophysiological test battery

The ABRs, oVEMP responses, and cVEMP responses were obtained from all controls. All response parameters were normal, including wave morphology, latency, and amplitude. In contrast, the

Table 1 The motor characters of Parkinson's disease patients

Motor symptoms	Mean ± SD (range)
H&Y off	2.73 ± 0.84 (2–5)
H&Y on	0.93 ± 0.59 (0–2)
S&E off	68.67 ± 22.30 (50–90)
S&E on	90.0 ± 9.26 (70–100)
UPDRS-I off	3.33 ± 2.13 (0–6)
UPDRS-II off	12.73 ± 7.49 (0–27)
UPDRS-III off	30.20 ± 17.49 (2–69)
UPDRS-IV off	0.67 ± 1.40 (0–4)
UPDRS-total	41.33 ± 30.20 (2–109)

H&Y, Hoehn and Yahr Scale; off, medication off state; on, medication on state; S&E, Schwab and England Scale; UPDRS, Unified Parkinson's Disease Rating Scale.

Table 2 Mean, SD, range, and *t* and *P* values of PTA thresholds (dBHL) in ears of the study groups

	PD			Control group			*t*	*P*
	Mean	SD	Range	Mean	SD	Range		
250^0Hz								
Right	25	10.4	15–50	19.3	3.7	15–25	1.9	0.06
Left	21	6	15–35	19.3	3.7	15–25	0.9	0.37
500^0Hz								
Right	23.3	12.3	10–60	18.7	4.8	10–25	1.3	0.18
Left	19.6	7.2	10–35	18.3	5.2	10–25	0.5	0.57
1000^0Hz								
Right	27.3	12.1	10–45	21	5.7	10–30	1.8	0.08
Left	24.3	10.7	10–45	20.3	5.8	10–25	1.3	0.21
2000^0Hz								
Right	28.3	13.9	10–50	21.3	6.1	10–30	1.8	0.09
Left	25.7	13.9	10–50	20	7.0	10–30	1.4	0.173
4000^0Hz								
Right	38.7	17.1	15–85	26.7	6.9	15–40	2.5	0.02*
Left	36	17.4	15–65	24.7	6.4	15–30	2.4	0.03*
8000^0Hz								
Right	47	20.6	15–80	33.7	9.7	15–50	2.3	0.03*
Left	44.7	24.9	15–85	27.7	7.9	15–40	2.5	0.02*
WRS%								
Right	92.3	9.5	68–100	96.0	3.4	92–100	−1.4	0.16
Left	93.3	6.9	80–100	96.5	3.3	92–100	−1.6	0.12

PD, Parkinson's disease; WRS%, word recognition score %. *Statistically significant.

majority of PD patients showed either absent or altered responses in at least one of the parameters in the applied test battery (Fig. 1).

ABR was elicited in all ears of PD patients, except in one ear, which did not show any response. The absolute latencies of wave V and I–V interpeak latencies were prolonged on stimulation of ears ipsilateral and contralateral to the CMA side (Table 3). Moreover, ipsilateral to the CMA side, the absolute latency of wave III and the interpeak I–III were also seen prolonged. The difference in latency measures between the two study groups was statistically significant ($P=0.03$ or 0.04). The interaural latency difference in PD patients was statistically insignificant between ears ipsilateral and contralateral to the CMA side ($P=0.2$).

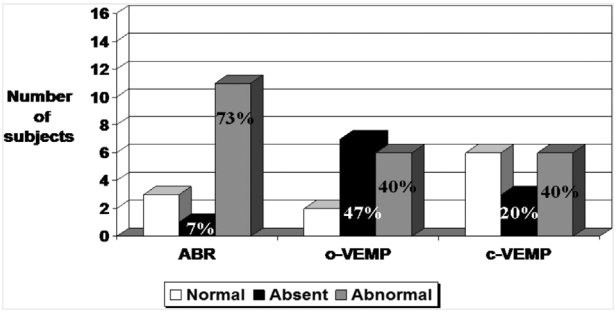
Fifty-three percent of PD patients ($n=8$) had an abnormal ABR wave morphology. Bilateral abnormality was seen in three (20%) patients. The remaining five (33%) patients had unilateral abnormal morphology contralateral to the CMA motor side. The difference between the two study groups in wave morphology reached statistically significant difference ($Z=-2.693$, $P=0.007$).

Furthermore, 10 (67%) PD patients showed clear ABRs only at high intensity (90^0dBnHL) with fair ABR wave resolution at lower intensities. This abnormality was bilateral in four patients, contralateral to the CMA side in four patients, and ipsilateral in two patients. The difference in wave morphology was statistically significant between the two study groups (Z value contralateral $=-3.5$, $P=000$; ipsilateral $=-2.6$, $P=0.007$). Normal latency/rate function was seen in PD patients except in two patients with abnormality in the ear contralateral to the CMA side. At the end, it was obvious that the ABR abnormalities were mainly seen either bilateral or in ears contralateral to the CMA side.

Ocular vestibular evoked myogenic potential

Absent oVEMP responses were the most common abnormality. It was seen in 47% of PD patients ($n=7$), bilateral in three patients and unilateral in four patients (two ipsilateral to the CMA side and two contralateral to the CMA side). In PD patients with preserved oVEMP, the latencies of n1 and p1 were prolonged when compared with the age-matched control group contralateral to the CMA

Figure 1



Summary of electrophysiological test results in PD subjects.

Table 3 Mean, SD, range (ms), and *t*-test of the auditory brainstem responses at 90^0dBHL in the Parkinson's disease and control group

	PD			Control group			*t*	*P*
	Mean	SD	Range	Mean	SD	Range		
Wave I								
Ipsi	1.56	0.08	1.4–1.8	1.45	0.09	1.4–1.6	1.7	0.10
Contra	1.58	0.11	1.4–1.6	–	–	–	2.1	0.06
Wave III								
Ipsi	3.8	0.30	3.3–4.7	3.6	0.14	3.4–3.7	2.4	0.03*
Contra	3.7	0.34	3.4–4.6	–	–	–	1.5	0.15
Wave V								
Ipsi	5.9	0.45	5.3–6.9	5.6	0.18	5.4–5.8	2.1	0.04*
Contra	5.8	0.41	5.4–7	–	–	–	2.1	0.04*
I–III								
Ipsi	2.1	0.23	1.8–2.6	2.1	0.12	1.8–2.2	1.5	0.15
Contra	2.0	0.33	1.7–2.5	–	–	–	–0.27	0.78
III–V								
Ipsi	2.1	0.24	1.9–2.6	1.9	0.17	1.7–2.2	2.2	0.036*
Contra	2.0	0.23	1.7–2.5	–	–	–	1.2	0.25
I–V								
Ipsi	4.3	0.33	3.6–5.0	4.0	0.18	3.8–4.2	2.4	0.025*
Contra	4.2	0.34	4.0–4.8	–	–	–	2.2	0.03*

Contra, contralateral (to clinically more affected side); Ipsi, ipsilateral; PD, Parkinson's disease. *Statistically significant.

side (Table 4). In PD patients, the n1–p1 amplitude was reduced bilaterally with large mean IAD ratio compared with the control group. The difference between the two study groups was statistically significant.

Cervical vestibular evoked myogenic potential

In contrast to the oVEMP, the cVEMPs were clearly recorded in 80% PD patients ($n=12$). The P13 and N23 were absent in two and one patients contralateral and ipsilateral to the CMA side, respectively. In the remaining patients, statistically significant alterations were seen in P13 and N23 latencies, amplitudes, and IAD ratio either ipsilateral or contralateral to the CMA side. The alterations were in the form of prolonged latencies, reduced P13–N23 amplitude, and with greater asymmetry ratio compared with the control group (Table 5).

On comparing the results of oVEMP and cVEMP on the two sides (ipsilateral and contralateral to the CMA side), no statistically significant difference was seen.

Auditory brainstem evoked responses, vestibular evoked myogenic potentials, and motor Unified Parkinson's Disease Rating Scale scores

The motor UPDRS scores during the medication 'off' state were correlated with the electrophysiological test battery as follows. The absolute latencies of wave III and wave V contralateral to the CMA side were significantly correlated to disease severity H&Y and rigidity. Furthermore, the absence of ABR waves contralateral to the CMA side was significantly correlated to S&E, UPDRS-III, and rigidity (Table 6).

The abnormal cVEMP responses contralateral to the CMA side showed a significant correlation with H&Y off disease stage ($P=0.013$), UPDRS-III ($P=0.045$), rigidity ($P=0.027$), and bradykinesia 'off' scores ($P=0.026$). The cVEMP P13 and N23 wave latencies ipsilateral to the CMA side were also correlated to dyskinesia scores ($P=0.01$ and 0.027). Nevertheless, the oVEMP responses ipsilateral to the CMA side showed moderate correlation with a trend to significance with UPDRS-III, rigidity, and axial off scores (Table 6).

Table 4 Mean, SD, range, and *t*-test of the ocular vestibular evoked myogenic potential absolute latencies (ms), amplitude (μV), and asymmetry ratio (%) in both study groups

	PD			Control group			*t*	*P*
	Mean	SD	Range	Mean	SD	Range		
N1								
Ipsi	11.7	1.8	10–15	11.5	0.4	10.8–11.9	0.61	0.54
Contra	12.3	1.5	9.5–14	–	–	–	2.07	0.04*
P1								
Ipsi	17.2	4.8	14–27.5	15.8	0.36	15.2–16.8	1.69	0.10
Contra	17.8	2.3	12–21.8	–	–	–	2.4	0.025*
N1–P1 amplitude								
Ipsi	5.7	3.9	1.9–16.8	15.6	3.5	4.5–19.5	–7.2	0.00*
Contra	5.8	4.4	1.5–8	–	–	–	–5.9	0.00*
Asymmetry ratio (%)	27.5	25.3	2.8–49	3.2	1.2	1–8.5	3.84	0.001*

Contra, contralateral (to clinically more affected side); Ipsi, ipsilateral PD, Parkinson's disease. *Statistically significant.

Table 5 Mean, SD, range, and *t*-test of the cervical vestibular evoked myogenic potential absolute latencies (ms), amplitude (μV) and asymmetry ratio (%) in both study groups

	PD			Control group			*t*	*P*
	Mean	SD	Range	Mean	SD	Range		
P13								
Ipsi	16.5	0.55	15.1–17.8	14.6	1.7	12.1–14.9	–2.1	0.04*
Contra	16.5	0.8	9.5–14	–	–	–	–3.5	0.001*
N23								
Ipsi	24.2	0.53	14–27.5	23.0	2.1	23.1–25	–1.5	0.142
Contra	24.4	0.7	12–21.8	–	–	–	–2.1	0.04*
P13–N23 amplitude								
Ipsi	3.2	1.2	6.2–8.8	13.8	4.4	3.7–18.8	8.9	0.000*
Contra	3.2	1.2	5.1–21	–	–	–	6.2	0.000*
Asymmetry ratio (%)	21.9	12.9	3.2–46.3	3.2	1.2	0.5–7.5	5.6	0.000*

Contra, contralateral (to clinically more affected side); Ipsi, ipsilateral; PD, Parkinson's disease. *Statistically significant.

Table 6 The significant correlations between vestibular evoked myogenic potential, auditory brainstem evoked responses, and motor Unified Parkinson's Disease Rating Scale scores in medication 'off' state

	cVEMP					oVEMP		ABR		
	Ipsilateral		Contralateral			Ipsilateral		Contralateral		
	P13	N23	Absence	N23	P13–N23 amplitude	n1	p1	Absence	Wave III	Wave V
H&Y off										
r value	–	–	–	–	**0.689***	–	–	–	0.61*	0.53*
P value	–	–	–	–	**0.013**	–	–	–	**0.028**	**0.043**
S&E off										
r value	–	–	–	–	–	–	–	0.665**	–	–
P value	–	–	–	–	–	–	–	**0.007**	–	–
UPDRS-III off										
r value	–	–	–0.523*	–	–	0.64*	–	–0.54*	–	–
P value	–	–	**0.045**	–	–	**0.046**	–	**0.037**	–	–
Rigidity off										
r value	–	–	–	0.63*	–	0.63	0.63	–0.77**	–	0.54*
P value	–	–	–	**0.027**	–	0.05	0.05	**0.001**	–	**0.039**
Bradykinesia off										
r value	–	–	–0.571*	–	–	–	–	–	–	–
P value	–	–	**0.026**	–	–	–	–	–	–	–
Axial off										
r value	–	–	–	–	–	–	0.635*	–0.640*	–	–
P value	–	–	–	–	–	–	**0.049**	**0.010**	–	–
Dyskinesia										
r value	0.71**	0.63*	–	–	–	–	–	–	–	–
P value	**0.01**	**0.027**	–	–	–	–	–	–	–	–

ABR, auditory brainstem evoked responses; contra, contralateral (to clinically more affected side); cVEMP, cervical vestibular evoked myogenic potential; H&Y, Hoehn and Yahr Scale; Ipsi, ipsilateral;; 'off', medication off state; oVEMP, ocular vestibular evoked myogenic potential; S&E, Schwab and England Scale; UPDRS, Unified Parkinson's Disease Rating Scale. *Statistically significant. **Statistical significance. Bold for statistical significance.

In contrast, the UPDRS-II, tremor, and S&E subscales showed no significant correlations with ABR and VEMPs responses. The duration of disease, age, and age of onset showed no correlation either with ABRs, cVEMP responses, and oVEMP responses.

Discussion

The current study showed age-dependent high-frequency hearing loss in PD patients compared with both normative values and values for healthy age-matched controls. Yýlmaz *et al.* [17] reported that PTA results were significantly elevated for PD patients in 4000 and 8000^{0}Hz. 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 [18].

It is feasible that the natural aging process combined with neurodegenerative changes intrinsic to PD might interfere with cochlear transduction mechanisms, thus anticipating presbycusis. α-Synuclein is located 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.* [19]. Synucleins are widely expressed synaptic proteins within the central nervous system and have been implicated in neurodegenerative disorders such as PD. Furthermore, Lai *et al.* [18] emphasized that, as dopamine is an important neurotransmitter that helps to protect the cochlea from noise exposure, its deficiency in PD can thus lead to damage to the cochlea and result in hearing loss.

The current study confirmed the impairment of ABRs and VEMP responses in patients with PD compared with controls that is related to characteristic clinical asymmetry of PD and its cardinal motor features. Consequently, it reflects brainstem pathology among PD patients at different levels and highlights the asymmetry of these changes.

The significant prolongation in ABR wave III and V latencies observed in the current study may, in fact, be a reflection of the postsynaptic activity in the structures where they are generated – these being the superior olive and in the vicinity of the inferior colliculus. Furthermore, an increase in auditory brainstem transmission time was shown from the prolonged I–V interpeak latency ipsilateral and contralateral to the CMA side. In the cochlear nucleus, spherical cells of the anterior part of the anteroventral cochlear

nucleus generate a part of wave III, whereas in the contralateral superior olivary complex, principal cells of medial nucleus of trapezoid body contribute to wave III generation. Ipsilateral and contralateral cells of the superior olivary complex participate in wave IV generation with medial superior olivary principal cells identified as wave IV generators. Cellular generators of wave V are located in the lateral lemniscus and or the inferior colliculus [20]. However, the neurotransmitter of these neurons is glutamate with excitatory effect and GABA or glycine with their inhibitory effects.

It is increasingly recognized that degenerating neurons in PD, such as dopaminergic neurons of the nigrostriatal pathway, do not live in isolation. These neurons receive a variety of afferents and are surrounded by a large number of nondopaminergic neurons like GABAergic and cholinergic neurons and non-neuronal cells such as astrocytes and microglia [6]. Thus, it is the current belief that the neurodegeneration in PD occurs in response to a mixture of deleterious mechanisms taking place both inside the degenerating neurons and outside the degenerating neurons. It is possible that this neurodegenerative process affects the functionality of central auditory pathway, leading to a prolongation of wave latencies and peak intervals of auditory evoked potentials. Alexa *et al.* [21] showed bilateral delay in ABR waves II, III, IV, V, and IPL III–V and concluded that the auditory system is involved equally on both sides, regardless of the asymmetry of motor manifestation.

Nevertheless, the abnormal ABR wave morphology and the fair resolution of ABR waves at lower intensities seen in the present study highlighted subtle auditory brainstem dysfunction. This dysfunction could be a sequel of disturbed neural synchrony of the brainstem as a result or as a part of the neurodegenerative process of PD. Similarly, Yousefi *et al.* [20] reported ABR waveform morphologies that differed markedly in relation to medication state and, indeed, from the typical morphology of the control group.

Both the oVEMPs and cVEMPs were profoundly affected in the studied PD patients compared with the controls. As the vestibulocollic and vestibulo-ocular reflex pathways diverge beyond the nerve root entry zone, oVEMPs and cVEMPs provide valuable localizing information in central disorders. Altered oVEMPs indicated early functional involvement of the upper brainstem compared with results of cVEMPs, reflecting the status of the lower brainstem [10]. The prolongation of oVEMP and cVEMP wave latencies has been attributed to slowing of conduction, possibly as a consequence of the degenerative process of PD. According to Bandini *et al.* [22], abnormal VEMPs are commonly found in patients with known brainstem involvement and are also able to detect 'silent' lesions.

The amplitudes of oVEMP and cVEMP in PD patients were reduced compared with the age-matched controls, suggesting reduced vestibular nuclei excitability within the brainstem. Recently, Seidel *et al.* [23] reported a direct disruption of vestibular nuclei by PD pathological changes. Other possible mechanisms include disrupted interconnections with degenerated other brainstem nuclei by PD pathology [24]. Although the IAD for both oVEMP and cVEMP did not exceed the 34% cutoff limit to be pathologic, their results should be interpreted cautiously. The presence of a high statistically significant difference in IAD between the PD patients and the age-matched control group might be an indication for the asymmetry within the tested vestibular pathway.

De Natale *et al.* [25] reported that the frequency of alteration of oVEMPs and cVEMPs in PD patients was 83.3% with the absence of responses being the prevalent alteration in PD. Pollak *et al.* [26] showed unilateral absent VEMP responses in 20 (37%) PD patients and bilateral absent responses in four (7.4%). Their PD patients with preserved peaks had normal latencies as compared with controls.

Interestingly, remarkable findings were observed in the current study when the main motor features of PD were correlated with ABRs and VEMP responses. Rigidity and bradykinesia were related to ABRs and cVEMP responses, whereas tremor was not. The correlations were mainly to the responses contralateral to CMA side, which is consistent with the asymmetric nature of PD pathology in the SN and their connections [3].

In addition, the correlations were confined to ABRs and cVEMPs and not 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 [6]. This explained the lack of correlation with auditory and vestibular responses. Moreover, recent animal studies demonstrated that brainstem structures such as pontine

nuclei and locus coeruleus are involved in the pathophysiology of L-dopa-induced dyskinesia [27]. This could explain the correlation seen in the present study between L-dopa-induced dyskinesia and cVEMPs wave latencies.

Although the correlation of ABR, oVEMP, and cVEMP were mainly to one side, no differences existed in all tests between the two sides. This could be attributed to the medication state of the patients. All PD patients underwent the tests during 'medication-on state', which masked the abnormalities between the two sides as recently reported by Pötter-Nerger *et al.* [28].

In contrast, previous studies reported lack of correlation with clinical motor scores [25,26]. They used the mean values of VEMP responses on both sides, not in relation with the CMA side, thus underestimating the potential asymmetry that could ameliorate abnormalities. Moreover, differences in experimental conditions during testing, age differences between cases and controls, and different clinical characteristics of recruited patients could explain the inconsistency in the results of different studies that addressed the vestibular functions in PD.

The current study had few limitations, especially small number of cases and variable disease severity of recruited patients. Thus, further studies with a larger number of patients and different disease stages are needed to reproduce current findings.

In conclusion, the abnormalities in ABR and VEMP responses were confirmed in PD patients similar to previous studies. These abnormalities reflected dysfunction of different levels of the brainstem and is consistent with caudal–rostral brainstem pathological changes as proposed by Braak *et al.* [5]. This conclusion does corroborate new considerations of a more widely distributed neurodegeneration model along the brainstem in PD. 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 remain to be determined. 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.

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Conflicts of interest

There are no conflicts of interest.

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