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Vestibular Evoked Myogenic Potential Abnormalities in Early and Late-Stage Parkinson Patients

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Abstract: Loss of balance can be seen in idiopathic Parkinson's disease. There are only a few studies in the literature in which brainstem involvement in IPD has been researched with neurophysiological tests such as vestibular evoked myogenic potential. In this study, it was investigated whether there is a difference in the results of vestibular evoked myogenic potential testing in early or late stage of idiopathic Parkinson's disease. The idiopathic Parkinson's disease cases were classified as early stage and late stage according to the Hoehn-Yahr scale. The presence of a positive wave with a latency of P13 and a negative wave with a latency of N23 was investigated as the first reflex response The latencies of these potentials and the absolute amplitude of the P13-N23 component were measured. The vestibular evoked myogenic potential results of the patients with early and late stage idiopathic Parkinson's disease were compared with those of the control group. The right P13 latency mean value in the late-stage patient group was significantly prolonged than in the early-stage patient group and the control group. The right P13-N23 amplitude mean value of the late and early-stage patient groups was significantly smaller than that of the control group ($p < 0.002$ and $p < 0.001$, respectively). Among the patients with idiopathic Parkinson's disease, the P13 latency was statistically increased in those with a fall history than in those without a fall history. As a result, this study indicates that the vestibular evoked myogenic potential pathway is affected over time especially in patients with late-stage Parkinson's disease. © 2023 NTMS.

Keywords: Parkinson; c VEMP; Neurophysiology; Brainstem.

1. Introduction

Parkinsonism is a chronic, progressive neurodegenerative disease characterized by restingtremor, rigidity, bradykinesia, and postural instability. The most common cause of parkinsonism is idiopathic Parkinson's disease. The main pathological changes in Parkinson's disease are the loss of melanin-containing dopaminergic neurons in the substantia nigra pars compacta (SNc) and the presence of Lewy bodies (LB) in surviving neurons, and Lewy neurites in axons. Immunohistochemical staining data show that Lewy bodies predominantly contain alpha-synuclein, ubiquitin, neurofilaments and many other different

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proteins [1]. The decrease in dopaminergic activity because of the degeneration occurring in dopaminergic neurons in the nigrostriatal pathway is the main cause of the disease. In a pathological study based on the accumulation of alpha-synuclein, Braak et al. asserted that the pathological process began in the olfactory bulb, caudal brainstem structures and even in the cardiac and gastrointestinal peripheral autonomic system long before the SN, comprised serotonergic, cholinergic, and noradrenergic neurons in the locus coeruleus, median raphe and nucleus basalis, and that widespread cortical involvement occurred in the progressive process [2, 3]. Clinical motor symptoms in IPD appear following a pre-clinical period of 4-6 years during which approximately 60 % of nigral dopaminergic neurons are lost [4]. In addition, motor symptoms, non-motor symptoms including depression, dementia, anxiety, psychosis, sleep disorders, autonomic dysfunction (symptomatic orthostatic hypotension, erectile dysfunction, micturition-defecation problems) are common in IPD, and many of these symptoms may also develop before the onset of motor symptoms. Parkinson's disease is considered to be the second most common neurodegenerative disorder after Alzheimer disease [4, 5]. As treatments that modify and perhaps prevent the disease become available, the importance of early diagnosis of Parkinson's disease in the preclinical or at least premotor phase will increase. For this reason, various studies are carried out for the development of non-invasive diagnostic methods and markers with high specificity and sensitivity. Recently, promising results have been achieved in ligand uptake-based neuroimaging techniques that demonstrate the integrity of the nigrostriatal pathway, and in marker studies performed in cerebrospinal fluid, blood, and salivary fluids [5]. Postural instability can be seen as a symptom in Parkinson's disease. This condition may indicate the deterioration of the vestibular system [6]. VEMP is one of the non-invasive and easily applicable electrophysiological tests that evaluate the inferior-vestibular nerve, brainstem and central connections starting from the saccule and macula [6]. There are studies involving the use of VEMP in diseases particularly affecting the brainstem such as multiple sclerosis, migraine, progressive supranuclear palsy, and olivopontocerebellar atrophy [7-9]. However, few studies have been conducted about VEMP in the context of evaluating the presence of brainstem pathology in IPD [7, 10, 11]. In the later stages of Parkinson's disease, loss of balance and falls can be seen due to brainstem involvement [12]. Therefore, we aimed to investigate whether vestibular functions are impaired in early and late-stage Parkinson patients through VEMP testing as neurophysiological.

2. Material and Methods

This study was carried out in the Neurophysiology Laboratory of the Neurology Department at Inonu University between January 2013 and March 2013. Before beginning the study, an ethical approval was obtained from the Local Ethics Committee of İnönü University Faculty of Medicine. In this study, 55 patients followed up with the diagnosis of IPD in the Movement Disorders Outpatient Clinic of the Department of Neurology of Inonu University, and 24 age- and gender-matched healthy volunteers as the control group were enrolled. The IPD patients were grouped as early stage and late stage according to Hoehn-Yahr staging. All patients and healthy volunteers were informed about the method and purpose of the study, and each participant signed an informed consent form. The patients with IPD were questioned in terms of brainstem symptoms, and it was purposed to assess whether the VEMP test could provide a diagnostic contribution especially in the early stage.

The patients and healthy volunteers were examined via otoscope before the VEMP examination especially in terms of neck movements. The patients with abnormal otoscopic examination or problems in neck movements, those with hearing threshold above 20 dB and conductive hearing loss in the audiometric test were not included in the study.

The room in which the examination was performed was well ventilated, dimly lit, and kept at a constant temperature of 25 °C. During the recording, the subjects were asked to be relaxed but awake, and to look at a fixed point with their eyes open. A click sound was given to the ear with the help of auditory stimulus to evoke VEMP. The inclusion criteria for the study were determined separately for each group. In the IPD group, the patients with definite diagnosis of idiopathic Parkinson's disease according to the diagnostic criteria established by Hughes et al. and those without clinical or electrophysiological peripheral neuropathy that could affect VEMP testing were included in the study. In the control group, the subjects who did not have any complaints and had normal neurological examination were enrolled in the study.

2.1. *VEMP Protocol*

The VEMP examination was performed with the Medtronic EMG-EP device (version 4.3.505.0-Model 190B6). The examination was performed while the participant was asked to turn her/his head to the opposite side of the stimulated ear and always hold it in that position. For the combined muscle activation potential (CMAP) recording in VEMP examination, the active surface electrode was placed on the upper 1/3 of the sternocleidomastoid (SCM) muscle, the reference electrode was placed on the sternum, and the ground electrode was placed on the forehead region. The recording electrode impedances were kept below 5 ohms. The filter settings were adjusted to 10 Hz-3 KHz. A sound stimulus was given to each ear with headphones to evoke VEMP. The stimulus was a high intensity (105 dB HL) rarefaction click with a duration of 0.1 ms and a frequency of 3 s^{-1}. The procedure was

performed at least twice to ensure reproducibility in each ear and 128 CMAPs were averaged. Since high-intensity sound was used, a special attention was paid to the placement of the headphones during the recording.

The presence of a positive wave with a latency of approximately 13 ms (P13) and a negative wave with a latency of approximately 23 ms (N23) were investigated as the first reflex response in the VEMP examination. The latencies of these potentials were determined with the marker. The absolute amplitude of the P13-N23 component was measured.

2.2. Statistical Analysis

The "IBM SPSS Statistics Ver. 20 for MAC" statistical software package was used for statistical analyses of the data. In the statistical evaluation, the chi-square test for categorical variables, Student's t-test for continuous variables, and multiple logistic regression analysis for correlation analysis were performed.

3. Results

The ages of the patients ranged from 47 to 84 (Mean±SD: 66.95±8.83) and showed no statistical difference with the control group. Thirty-four of the patients were male, and 21 were female, and the gender distribution between the patients and healthy controls was similar (Table 1). Of the patients with IPD, 26 were in early stage and 29 was in late stage according to the Hoehn-Yahr staging.

Table 1: Age, gender and VEMP values of the Parkinson patients and control group.

	Control n=24	IPD patients n=55	p-value
Age	63.38±8.90	66.95±8.83	0.108*
Gender F/M	11/13	21/34	0.347**
Right P13 latency (ms)	13.48±2.03	14.14±2.58	0.227*
Right N23 latency (ms)	18.45±3.03	19.11±3.46	0.392*
Left P13 latency (ms)	14.55±2.74	14.39±2.44	0.812*
Left N23 latency (ms)	19.12±3.27	19.43±3.20	0.702*
Right P13-N23 amp (μV)	7.52±5.43	3.63±3.04	0.003*
Left P13-N23 amp (μV)	7.35±6.45	4.99±4.33	0.110*

*t test, ** chi-square test.

There was no significant difference between the Parkinson patients and the control group in terms of the mean values of right and left VEMP P13 wave latency (p=0.227, p=0.812, respectively) and N23 wave latency (p=0.392, p=0.702, respectively). The right and left P13-N23 amplitudes of the Parkinson patient group were lower than those of the control group. However, this difference was statistically significant only for the right P13-N23 amplitude.

The Parkinson patients were evaluated by grouping them according to the presence of falls. It was determined that falls were present in 29 patients (Table 2). Among the patients with IPD, the P13 latency was statistically higher in those with a fall than in those without a fall (13.37±2.36, 14.83±2.61, p=0.034).

Table 2: VEMP Values According to the Presence of Falling Symptom in the Parkinson Patients.

	No fall n=26	Fall n=29	p-value*
Age (years)	64.23±8.13	69.38±8.86	0.029
Right P13 latency (ms)	13.37±2.36	14.83±2.61	0.034
Right N23 latency (ms)	18.90±3.62	19.31±3.37	0.668
Left P13 latency (ms)	14.37±2.14	14.42±2.72	0.942
Left N23 latency (ms)	19.26±2.96	19.58±3.44	0.718
Right P13-N23 amp (μV)	3.25±2.70	3.97±3.34	0.383
Left P13-N23 amp (μV)	5.31±4.56	4.70±4.17	0.610
Disease duration (month)	49.00±47.15	70.48±43.92	0.087

* t test.

The late-stage patient group was statistically older than the early-stage patient group and control group (ANOVA test p=0.025, post hoc LSD test p=0.030 and p=0.014, respectively). The right VEMP P13 mean latency value in the late-stage patient group was statistically significantly prolonged than in the early-stage patient group and control group (ANOVA test p=0.043, post hoc LSD test p=0.025 and p=0.042, respectively). The mean amplitude value of the right VEMP P13-N23 in both the late stage and early-stage patient groups was statistically significantly lower than in the control group (ANOVA test p=0.000, post hoc LSD test p=0.002 and p=0.000, respectively). There was no statistically significant difference between the early-stage patient group, late-stage patient group and control group in terms of other VEMP parameters.

There was no statistically significant difference between the patient groups divided according to the presence of fall symptoms in terms of VEMP parameters and age (Table 3).

The Parkinson patients were grouped according to the presence of dementia. Dementia was present in six patients. A statistically significant difference was found between these patient groups in terms of VEMP parameters and age (Table 4).

Table 3: Age, gender and VEMP values of early and late-stage Parkinson patient groups and control group.

	Control n = 24	Early stage n = 26	Late Stage n =29	p-value*
Age (year)	63.38±8.90	64.23±8.13	69.38±8.86	0.025
Right P13 latency (ms)	13.48±2.03	13.37±2.36	14.83±2.61	0.043
Right N23 latency (ms)	18.45±3.03	18.90±3.62	19.31±3.37	0.651
Left P13 latency (ms)	14.55±2.74	14.37±2.14	14.42±2.72	0.967
Left N23 latency (ms)	19.12±3.27	19.26±2.96	19.58±3.44	0.870
Right P13-N23 amp (μV)	7.52±5.43	3.25±2.70	3.97±3.34	0.000
Left P13-N23 amp (μV)	7.35±6.45	5.31±4.56	4.70±4.17	0.156

*Anova test.

Table 4: VEMP values according to the presence of dementia in the Parkinson patients.

	No dementia group n = 49	Dementia group n = 6	p-value*
Age (year)	66.10±8.64	73.83±7.83	0.042
Right P13 latency (ms)	13.81±2.32	16.90±3.14	0.005
Right N23 latency (ms)	18.69±3.18	22.57±4.08	0.008
Left P13 latency (ms)	14.24±2.33	15.62±3.20	0.196
Left N23 latency (ms)	19.20±3.12	21.25±3.54	0.141
Right P13-N23 amp. (μV)	3.60±2.92	3.87±4.29	0.840
Left P13-N23 amp. (μV)	4.68±3.93	7.46±6.76	0.139
Disease duration (month)	57.55±45.46	83.00±51.53	0.207

* t test.

4. Discussion

Postural instability is one of the characteristic features of IPD. Injuries may occur due to falls and even disability may develop. Postural instability depends on inappropriate interaction between visual, proprioceptive, and vestibular signals [13]. In the vestibular system, the semicircular canals, utricle, and saccule in the inner ear pertain to balance. Semicircular canals assist in detecting angular motion. While the channels ensure the kinetic balance of the body, the utricle and the saccule help in perceiving linear motion and provide static balance. The utricle responds to gravity and to linear acceleration, especially in the horizontal plane. In addition, the saccule responds to linear acceleration in the foreground/background with vibrational type stimuli. Its contribution to stability and vestibular function integrity has been addressed in many studies. These studies can be listed as caloric test and rotational chair test, tilt-table, and galvanic stimulation of the vestibular system [7].

The VEMP test is an indirect test that evaluates the operation of a neuronal pathway that begins from the saccule and terminates in the SCM muscle. In other words, it neuroanatomically detects major brainstem circuits. It is thought that it examines mostly the saccular part of the vestibulospinal pathway. De Natale et al. suggested that VEMP could be a reliable method for evaluating the brainstem in Parkinson patients [14]. Scarpa et al. reported the presence of hearing loss and cervical VEMP abnormalities in high-frequency tests in both Parkinson patients and patients with multisystem atrophy, even if the patients do not have auditory and vestibular complaints [15].

It has been shown that brainstem involvement occurs in the preclinical period (Phase 1-2) when non-motor symptoms occur before the emergence of cardinal clinical manifestations of Parkinson's disease. Hence, we considered that the VEMP test might also be abnormal in early-stage Parkinson patients compared to healthy controls, and we investigated this situation in these patients. In our study, we found that the VEMP latencies in the early-stage Parkinson patients were like those of the control group, whereas there were small differences in the VEMP amplitude. However, we detected statistically significant VEMP abnormalities in the late-stage Parkinson patients than in both the control group and the early-stage Parkinson patients. Consequently, our findings indicate that VEMP impairment is more pronounced after the progression of the pathology in the brainstem in IPD.

In the study conducted with 54 IPD patients and 53 healthy controls, Pollak et al. investigated the correlation of VEMP with age, gender, disease characteristics (associated factors such as duration and stage of the disease, as well as the presence of dementia, depression, motor fluctuation, falls, dyskinesia, and psychosis) and treatment modalities. It was reported that in the IPD group, the unilateral VEMP response in 37% and bilateral response in 7.4% of the patients were not obtained. Among the patients whom the VEMP response was not obtained, 15 out of 24 patients had depression. Fifty percent of the patients without bilateral VEMP response received antidepressant treatment. It was found that there was a correlation between VEMP abnormalities and patients with depression and therefore receiving antidepressant treatment; nevertheless, there was no correlation between VEMP results and other clinical parameters [7].

In this study, there was no significant difference between the IPD group and the control group in terms

of the right and left side P13 latency and N23 latency. Although the left P13-N23 amplitude was smaller in the Parkinson patients than in the healthy controls, this difference was not statistically significant. The right P13-N23 amplitude was statistically significantly decreased in the Parkinson patients compared to the control group. Again, the right P13-N23 amplitude was statistically significantly smaller in the early-stage Parkinson patient group compared to the late-stage Parkinson patient group. It was detected that the right P13 latency was statistically significantly prolonged in the late-stage Parkinson patient group compared to the early-stage Parkinson patient group and control group.

In a study in which VEMPs in Parkinson patients and patients with progressive supranuclear palsy (PSP) were compared, a higher number of VEMP abnormalities were detected in patients with PSP, and it was suggested that the central vestibular pathways were more severely damaged in PSP than in Parkinson's disease [10]. In another study, Venhovens et al. investigated the value of VEMP as a neurovestibular test in predicting falls that may occur in the future among patients with Parkinson's disease and atypical parkinsonism. In these patients, positive predictive value of fall probability was obtained as 68% in the case of unilateral abnormal VEMP test and 83 % in the case of bilateral abnormal VEMP test [11]. In our study, similar to these previous studies, VEMP abnormalities were detected in the IPD patients with fall history.

Ampar et al. examined brainstem auditory evoked potentials and VEMP to investigate brainstem function in Parkinson patients. They found brainstem auditory evoked potentials and VEMP abnormalities in Parkinson patients, similar to our findings. They also reported that cervical VEMP abnormalities were correlated with symptoms of brainstem degeneration such as postural instability [16]. Hawkins et al. determined that advanced age, impaired proprioception, abnormal head impulse test and abnormal cervical VEMP results were correlated with deterioration in balance performance in Parkinson patients [17]. We similarly detected that there were pronounced VEMP abnormalities in the advanced stage of the disease. In a study investigating the static and dynamic otolith function and the absence of VEMP response in Parkinson patients, the absence of bilateral cervical VEMP has been found to be associated with a history of falling attacks [18]. Likewise, in another study, REM sleep behavior disorder and postural instability have been found to be correlated with VEMP abnormalities in Parkinson patients [19].

Shalash et al. studied cervical VEMP in 15 Parkinson patients and detected that cervical VEMP abnormalities of patients were significantly different than those of the control group. They stated that there were vestibular and auditory abnormalities in Parkinson patients and revealed the relationship between motor and non-motor features of the disease and brainstem dysfunction. In addition, they reported that vestibular potential abnormalities were associated with the severity and stage of the disease and recommended further studies to be conducted since VEMP may be a potential marker, especially in early-stage IPD [20]. In this study, we detected that the right VEMP P13 latency mean value in the late-stage patient group was statistically significantly prolonged than in the early-stage patient group and the control group. The right VEMP P13-N23 amplitude mean value in both the late stage and early-stage patient groups was statistically significantly smaller than in the control group. These findings indicate that the impairment in VEMP results is more pronounced in late-stage Parkinson patients, and that vestibular functions are impaired especially in advanced-stage Parkinson patients. In this study, we found that the VEMP latencies of the early-stage Parkinson patients were similar to those of the healthy controls, but there were some minor VEMP amplitude abnormalities. However, the clinical significance of these abnormalities is very limited, and thus vestibular function impairment increases in the late stage compared to the early stage of the disease.

5. Conclusions

Pronounced VEMP abnormalities were detected in the late-stage Parkinson patients. These findings show that the inferior-vestibular nerve, brainstem, and central pathway, starting from the saccule, are affected over time, especially in late-stage Parkinson patients.

Limitations of the Study

The limitations of the study is small sample size.

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Conflict of Interests

The authors declare no conflict of interest.

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Author Contributions

Conceived and designed the experiments; B.V., C.A., S.Y., K.A, O.Ç. Analyzed and interpreted the data; B.V., K.A, O.Ç. Contributed reagents, materials, analysis tools or data; B.V., C.A, S.Y., K.A, O.Ç. Wrote the paper; B.V., C.A, S.Y.

Ethical Approval

Ethics committee approval no. 2013/28 was received for this study from the ethics committee of Malatya İnönü University Faculty of Medicine Dean's Office.

Data sharing statement

All data relevant to the study are included in the article.

Consent to participate

Consent for the study was obtained from all participants for the study.

Informed Statement

The patient and control group who agreed to participate in the study signed the informed consent form.

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