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VISUAL AND BRAINSTEM AUDITORY-EVOKED POTENTIALS CORRELATE WITH SPECIFIC MOTOR AND NON-MOTOR SYMPTOMS IN PARKINSON'S DISEASE

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Abstract

Parkinson's disease (PD) is a common and complex neurodegenerative disease characterized by progressive motor and non-motor symptoms. The current study investigated the dysfunction of brain hemispheres and brainstem of PD patients and its relation to motor and non-motor symptoms using brainstem auditory evoked potentials (BAEP) and pattern reversal visual evoked potentials (p-VEP). We hypothesized that some motor and non-motor symptoms of PD due to specific dysfunctions of brainstem and brain hemispheres could be related to changes in p-VEP and BAEP. Accordingly, the aim of this study was to explore the abnormalities of BAEPs and p-VEPs in patients with PD and its correlation to the motor and non-motor symptoms of PD. Seventy-six nondemented PD patients took part in the p-VEP evaluations and 66 nondemented PD patients were included in BAEP evaluation. In order to compare the p-VEP performance of PD group, we included a control group comprising 32 age-matched participants. A BAEP substudy involved 29 age-matched healthy controls. All patients underwent a comprehensive motor and non-motor neuropsychological assessment. We found significant changes in all tested parameters of p-VEPs in PD patients compared to control subjects. In addition, these lower scores in p-VEP correlate with the results of some tests for cognition related to frontal-striatal dysfunction and contralateral rigidity, but not with the results of overall motor evaluation or other non-motor symptoms studied. In BAEP, PD patients have a significant prolongation of III and V wave

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latencies compared to controls. In addition, when examining the possible associations of BAEP with other non-motor manifestations of the disease, such association was observed only by the apathy scale. In conclusion, the current study confirms the visual and auditory abnormalities among PD patients that reflect brain hemispheres and brainstem pathological changes. It also correlates these abnormalities to some motor and non-motor features of the disease, providing a localizing tool for associated brain hemispheres and brainstem dysfunctions. Furthermore, abnormal visual evoked potentials are associated with motor and non-motor symptoms due to the basal ganglia dysfunction. In contrast, abnormal auditory evoked potentials are connected with apathy, which is considered to be related with brainstem raphe nuclei dysfunction.

Key words: Parkinson's disease, evoked potentials, clinical symptoms

Introduction. Parkinson's disease (PD) is a common and complex neurodegenerative disease traditionally characterized by progressive motor symptoms, including bradykinesia, rigidity, and tremor [1]. However, PD is also associated with numerous non-motor symptoms (NMS), such as cognitive impairment, neuropsychiatric symptoms, sleep disorders, and others, which could have a greater impact on quality of life than motor symptoms and are significantly associated with reduced well-being [2,3]. Lewy bodies (LB) and Lewy neurites (LN) composed of alpha-synuclein are the pathological hallmarks of PD [4]. Alpha-synuclein pathology related to non-motor symptoms was described in brain hemispheres, brainstem, spinal cord, and peripheral nervous system [5], as well as in substantia nigra and other brainstem nuclei for motor symptoms.

Neurophysiological studies, namely pattern reversal visual evoked potentials (p-VEP) and brainstem auditory-evoked potentials (BAEP), are inexpensive and commonly accessible non-invasive techniques that allow the evaluation of functional changes of the visual and auditory pathways sensitivity in brain hemispheres and brainstem.

In the current study, we hypothesized that some motor and non-motor symptoms of PD due to specific dysfunctions of brainstem and brain hemispheres could be related to changes in VEP and BAEP. Accordingly, the aim of this study was to explore the abnormalities of BAEPs and VEPs in patients with PD and its correlation to the motor and non-motor symptoms of PD.

Patients and methods. Patients were recruited from participants who sought consultation at the University Hospital "Alexandrovska" in Sofia, because of Parkinsonian signs and for the treatment of their parkinsonism, as well. The research was approved by the ethics committee of the Medical University-Sofia, and all participants provided written informed consent prior to their involvement in the study. The evaluation procedure consisted of detailed medical history, physical and neurological examinations, cognitive and other non-motor features evaluations, appropriate laboratory tests, neuroimaging (brain computed tomography or magnetic resonance imaging) and short-latency evoked potentials (pattern Visual

Evoked Potentials (p-VEP) and Brainstem Auditory Evoked Potentials (BAEP)). History of medical, neurological, psychiatric and other non-motor problems was obtained from the patient and family members (usually the patient's spouse or children). Global cognitive status and cognitive staging was evaluated by the Mini-Mental State Examination (MMSE), Mini-Mental Parkinson (MMP) and Mattis Dementia Rating Scale (DRS). Among the 178 patients meeting the UK Parkinson's disease Society (UKPDS) Brain Bank criteria for PD, 102 patients were excluded from p-VEP study because of the following: (1) patients with coexisting dementia (according to MDS criteria for PD dementia [6]; (2) patients with uncorrected visual deficit; (3) other ophthalmologic diseases. For BAEP study another group of 10 PD patients was excluded due to auditory diseases. Finally, 76 nondemented PD patients took part in the p-VEP evaluations and 66 nondemented PD patients were included in BAEP evaluation. In order to compare the p-VEP performance of PD group, we included a control group comprising 32 age-matched participants without history or symptoms of psychiatric/neurological disease and without ophthalmologic diseases. A BAEP substudy involved 29 age-matched healthy controls (three subjects were excluded due to auditory diseases).

Detailed cognitive evaluation of PD group included a neuropsychological battery. Episodic memory was assessed by the Buschke Free and Cued Selective Reminding Test (FCSRT). Attention and executive functions were tested by the Trail Making Test part A and B, the Modified Card Sorting Test (MCST), digit span backward of the Wechsler Adult Intelligence Scale and the Stroop Test. Language abilities were determined by the 15-item subset of the Boston Naming Test, the semantic verbal fluency and the phonemic verbal fluency. Visuospatial abilities and constructional praxis were evaluated by the Clock Drawing Test, the ability to copy 5 complex designs and the interlocking pentagon copying item within the MMSE. The severity of parkinsonism and cardinal motor features (bradykinesia, rigidity, tremor and postural instability) in PD group were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr staging. Other non-motor features, including apathy (Apathy scale), depression (Beck Depression Inventory), sleepiness (Epworth sleepiness scale) and other (Non-Motor Symptoms Scale), as well as quality of life (Parkinson's Disease Questionnaire) were also evaluated.

P-VEP and BAEP were performed by using a Nihon Kohden evoked potentials response unit (Neuropack μ MEB-9102/9104 Nihon Kohden). For p-VEP a chessboard pattern with frequency of reversion of 1 Hz was used, the filter bandwidth was 1–100 Hz. Monocular foveolar ($15'$) were consistently applied. The duration of analysis was 500 msec. The active electrodes were positioned at O1, Oz and O2 according to International 10/20 system and the referent electrode was placed on Cz position. In each study, 100 averagings were conducted with at least two replications. In BAEP consistent monoaural click stimulation with intensity of 90 dB nHL and 60 dB masking noise of the contralateral ear was held. Filter

bands were 200 to 2000 Hz, stimulation frequency 10 Hz. Epoch analysis was 10 msec. At least two stimulations with 2000 averagings for each ear were applied. Recording electrodes were placed as follows: (1) on the scalp at the vertex (Cz position of the 10–20 International System of EEG electrode placement); and (2), over the left and right mastoid processes (M1 and M2 positions of the 10–20 System). The ground electrode was placed on the scalp in a midline frontal location (position Fz of the 10–20 System). Electrode impedance was < 5 KOhms. The findings of BAEPs and pattern reversal VEPs of PD patients were grouped to ipsilateral and contralateral to the clinically more affected (CMA) side and compared to the total of both sides of the control subjects.

Statistical analysis. Irregularly distributed data was analyzed using the Mann–Whitney test, normally distributed data were analyzed using unpaired two samples t-test, when PD patients were compared to normal controls. Comparison between ipsilateral/contralateral eye, as well as ipsilateral/contralateral hemisphere in PD group was performed with paired samples t-test. Pearson correlations between clinical (motor and non-motor) symptoms and abnormal components of visual/auditory evoked potential were evaluated in patients suffering from PD. Differences were interpreted as significant by at least $P < .05$. All analyses were computed using Statistical Package for the Social Sciences (SPSS) version 19.0 statistical software.

Results. ***Comparative characteristics of p-VEP between PD patients and control subjects.*** When comparing actual age (Table 1) no significant differences were observed between the groups of control subjects. In terms of the total (from both eyes) p-VEP (Table 1), PD patients showed significantly lower amplitudes of N75/P100 and P100/N145, as well as significantly higher latency of P100 compared to control subjects. In addition, the subsequent paired sample t-test did not detect significant differences in P100 latencies between the ipsilateral and contralateral eyes ($t = 0.389$; $P = 0.688$), and between the ipsilateral and contralateral hemispheres ($t = 1.043$; $P = 0.300$) in PD patients. Also, no interhemispheric differences were observed with respect to the amplitude of N75/P100 ($t = -0.045$; $P = 0.964$) as well as the amplitude of P100/N145 ($t = -0.592$; $P = 0.556$) in PD patients.

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Actual age and p-VEP parameters of PD patients and control subjects

Characteristics	Controls ($N = 32$)	PD ($N = 76$)	P
Age	60.5 (7.1)	63.2 (7.8)	0.15
Latency P100	213.8 (20.0)	249.3 (45.4)	0.00
Amplitude N75/P100	16.7 (11.5)	9.7 (6.8)	0.00
Amplitude P100/N145	16.7 (8.8)	8.6 (6.9)	0.00

The values are mean (SD)

Correlations between p-VEP and clinical symptoms in PD patients. In patients with Parkinson's disease, lower overall parameters in the p-VEP correlate with some clinical (motor and non-motor) characteristics. With regard to cognition in PD patients, a significant correlation was observed between global cognitive evaluation examined through MMP, on the one hand, and amplitudes of N75/P100 (Pearson correlation = 0.385; $P = 0.004$) and P100/N145 Pearson correlation = 0.295; $P = 0.029$), on the other. In the area of attention/executive functions (Table 2) in PD patients, a significant increase in P100 latency was observed with an increase in the number of perseverative MCST errors. Correlations between increases in Stroop test part 1 and increases in the N75/P100 and P100/N145 amplitudes have also been observed. In the area of episodic memory (Table 2) in PD patients a correlation between the decrease in the amplitudes of N75/P100 and P100/N145 and the decline in FCSRT free recall results has been observed, as well as between the increase in P100 latency and the decrease in free delayed FCSRT recall. No correlations of VEP with recognition, number of false recognition and intrusions were observed. In the area of language, the decline in

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Significant correlations between clinical (motor and non-motor) symptoms and changes in p-VEP in PD patients

Characteristics	Related P100 responses	Pearson correlation	P
MCST (perseverations)	Latency P100	0.316^*	0.037
	Amplitude N75/P100	−0.195	0.194
	Amplitude P100/N145	−0.032	0.834
Stroop test part 1	Latency P100	−0.256	0.062
	Amplitude N75/P100	0.295^*	0.027
	Amplitude P100/N145	0.341^*	0.010
FCSRT (free recall)	Latency P100	−0.198	0.130
	Amplitude N75/P100	0.318^*	0.012
	Amplitude P100/N145	0.281^*	0.027
FCSRT (free delayed recall)	Latency P100	-0.329^*	0.012
	Amplitude N75/P100	0.268^*	0.039
	Amplitude P100/N145	0.317^*	0.014
Semantic verbal fluency	Latency P100	−0.095	0.485
	Amplitude N75/P100	0.161	0.227
	Amplitude P100/N145	0.260^*	0.048
Phonemic verbal fluency	Latency P100	−0.239	0.085
	Amplitude N75/P100	0.171	0.212
	Amplitude P100/N145	0.277^*	0.040
Rigidity (contralateral)	Latency P100	0.100	0.463
	Amplitude N75/P100	-0.370^*	0.004
	Amplitude P100/N145	−0.192	0.148

Abbreviations: FCSRT – Free and Cued Selective Reminding Test; MCST – Modified Card Sorting Test; $^*P < 0.05$.

Table 3

Actual age and BAEP parameters of PD patients and control subjects

Chracteristics	Controls $N = 29$	PD $N = 66$	P
Age	62.8 (6.9)	62.9 (8.0)	0.98
Latency I wave	1.6 (0.1)	1.7 (0.2)	0.07
Latency III wave	3.7 (0.1)	3.9 (0.3)	0.00
Latency V wave	5.6 (0.1)	5.9 (0.3)	0.00
Interpeak interval I-III wave	2.1 (0.1)	2.2 (0.2)	0.07
Interpeak interval III-V wave	1.9 (0.1)	2.0 (0.2)	0.39
Interpeak interval I-V wave	4.0 (0.3)	4.2 (0.3)	0.06

The values are mean (SD)

semantic and phonemic verbal fluency is related to a decrease in the amplitude of P100/N145. No correlation between BNT results and p-VEP was observed. Also, no correlations between the parameters of p-VEP and visuo-spatial/ constructive skills tests and other non-motor manifestations were observed (through Beck Depression Inventory, Epworth sleepiness scale, Apathy scale, NMSS and PDQ 39). When examining cardinal motor symptoms as well as overall motor evaluation and motor stage of the disease (Hoehn & Yahr scale), the results of the analysis also showed no significant correlation with the indicators of the p-VEP except for the correlation between the decrease of the amplitude of the N57/P100 and the increase of rigidity of the contralateral (i.e., the less affected side). In addition, the subsequent paired sample t-test established significant differences in contralateral versus ipsilateral tremor ($t = -4.535$; $P = 0.0001$), as well as between contralateral versus ipsilateral bradykinesia ($t = -5.489$; $P = 0.0001$) in PD patients. Significant differences were also observed between the rigidity manifestation of contralateral and ipsilateral (i.e., more affected versus less affected) side ($t = -7.865$; $P = 0.0001$) in PD patients.

Comparative study of brainstem auditory evoked potentials (BAEP) in patients with Parkinson's disease and control subjects. When comparing the actual age (Table 3) no significant differences were observed between the groups of control subjects. Table 3 also presents the results of the overall averaged BAEP in PD patients and the controls. The subsequent non-pair t-test established that PD patients have significantly higher latency in III and V waves than controls.

Correlations between BAEP and clinical (motor and non-motor) symptoms in patients with Parkinson's disease. When examining the possible correlations of the results of global cognition tests (MMSE, MMP), as well as the individual areas of cognition (including attention/executive functions, episodic memory, speech and visuo-spatial/constructive skills) with observed prolonged la-

tencies of the III and V waves, the Pearson test showed no significant correlations. When examining the possible correlation of changes in III and V wave latencies with the manifestation of other non-motor symptoms, only a significant correlation between V wave prolongation (Pearson correlation = 0.380; $P = 0.042$) and increased apathy in PD patients was established. When examining the cardinal motor symptoms (tremor, bradykinesia, rigidity and postural instability), as well as the overall motor evaluation, the results of the analysis also showed no significant correlations with the latencies of III and V waves.

Discussion. The current study investigated the dysfunction of brain hemispheres and brainstem of PD patients and its relation to motor and non-motor symptoms using BAEPs and p-VEPs. We found significant changes in all tested parameters of p-VEPs in PD patients compared to control subjects. In addition, these lower scores in p-VEP correlate with the results of some tests for cognition and contralateral rigidity, but not with the results of overall motor evaluation or other non-motor symptoms studied.

With regard to cognition, PD patients indicated significant relationship between global cognitive evaluation (through MMP), on the one hand, and P100 amplitudes, on the other. Subsequent evaluation in different cognitive domains revealed that in PD patients, impairments in VEP are related to deteriorations in some aspects of attention/executive function, episodic memory and language, which are thought to be primarily associated with the frontal-striatal dysfunction [7]. Reference to attention/executive function in PD patients, with an increase in the number of MCST perseverative errors a significant increase in P100 latency was observed. Stroop test 1 relationships with P100 amplitudes were also observed. In the area of episodic memory, PD patients revealed relationship between impairments in episodic memory retrieval (i.e., in free recall but not recognition) with a decrease in P100 amplitudes and an increase in P100 latency. In the area of language, the decrease of semantic and phonemic fluency tests that are considered with high executive component, are associated with a decrease in P100/N145 amplitude, but no significant correlation of changes in VEP and naming, a cognitive function that is thought to be associated with a relatively low executive component [8]. In this study, we separated the VEP responses to ipsilateral and contralateral responses according to CMA side. This approach could reflect the expected asymmetrical brain hemispheres pathology of PD [9]. Previous studies confirmed the asymmetry of cardinal motor symptoms that often persists through the course of the disease. This clinical asymmetry is related to asymmetrical degeneration of dopaminergic neurons of substantia nigra, striatal dopaminergic receptors, and their cortical connections [9]. This could be explained by asymmetrical underlying pathological changes and the asymmetrical dopaminergic deficiency that contributes to some non-motor features along with other neurotransmitters [9]. With respect to motor disorders, as assumed, we found clearly demonstrated significant asymmetry in the three cardinal motor symptoms – bradykinesia, rigidity,

and tremor in our patients suffering from Parkinson's disease. However, no significant differences in the parameters of p-VEPs between the two eyes or between the two hemispheres of the contralateral and ipsilateral (i.e., lower to higher clinically demonstrated) side were observed. Our results show that there is no functional asymmetry in the visual system in PD patients, despite the obvious clinical motor asymmetry. Similar discrepancies between p-VEP and motor disorders have been observed by other authors [10]. In the subsequent analysis intended to study the possible relations between motor symptoms with changes in p-VEPs, we only established a relationship between a decrease in N75/P100 amplitude and an increase in the rigidity of the less affected side in the absence of correlation with other cardinal symptoms, as well as with the general motor evaluation of the disease. Isolated correlations with only separate motor symptoms but not with the overall motor evaluation, have been observed by other authors [10]. Based on various pathological, pharmacological and experimental data in humans and animals, it has been assumed that tremor, rigidity, and bradykinesia could be considered stronger dopaminergic manifestations of PD and vice versa that speech, posture, balance, and gait disorders are associated with other neurotransmitter systems in addition to dopamine, due to their relative refractiveness to L-Dopa therapy, especially in the middle and advanced stages of the disease [11]. Visual impairments have been reported as common non-motor symptoms in PD patients [12], which in some cases may even precede the onset of motor symptoms of the disease [13]. Visual evoked potentials are a useful non-invasive neurophysiological method for measuring the integrity of the entire visual path from the retina to the occipital cortex. In a study of PD patients, a number of authors found an increased latency of P100 wave in chessboard stimulation, suggesting a delay in visual processing [14].

In brainstem auditory evoked potentials, PD patients have a significant prolongation of III and V wave latencies compared to controls. In addition, when examining the possible associations of BAEP with other non-motor manifestations of the disease, such association was observed only by the apathy evaluation test. Apathy in PD patients is described as a symptom separate of depression [15], assuming that it may have a significant impact on quality of life. A transcranial sonography establishes a relation between changes in brainstem raphe nuclei and apathy in PD patients [16]. Hearing disorders in PD patients are considered more common than in the general population [17]. In addition to peripheral hearing impairment, recently various studies have also addressed auditory processing disorders in PD patients compared to controls [18, 19]. BAEP have been widely used to test the auditory system and to diagnose and localize pathology affecting the brainstem. Supposed generators for wave III are the cochlear nucleus or medial upper olivary nucleus and the lateral lemniscus, and electrical activity from the central nucleus of the hypothalamus is also possible for wave V [14]. In studies on PD patients, some authors have also reported prolonged III and V wave latencies

in the non-demented PD patients studied compared to controls [14] and others only in V wave latency and interpeak latency of the I-V wave [20].

In conclusion, the current study confirms the visual and auditory abnormalities among PD patients that reflect brain hemispheres and brainstem pathological changes. It also correlates these abnormalities to some motor and non-motor features of the disease, providing a localizing tool for associated brain hemispheres and brainstem dysfunctions. Furthermore, abnormal visual evoked potentials are associated with motor and non-motor symptoms due to the basal ganglia dysfunction. In contrast, abnormal auditory potentials are connected with apathy, which is considered to be related brainstem raphe nuclei dysfunction. However, further studies are warranted to reproduce the correlation of VEP and BAEP responses to the individual motor and non-motor symptoms of PD and their value as potential biomarkers at different stages of the disease.

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