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P300 Wave Changes in Patients with Parkinson's Disease

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ABSTRACT

Introduction: Parkinson's disease (PD) is chronic progressive neurodegenerative disease. In patients with Parkinson's disease among other symptoms occur cognitive dysfunctions, which can be shown by P300 wave changes. **Aim:** The aim of this study was to demonstrate that patients with Parkinson's disease have reduced amplitude and prolonged latency, longer than 300 ± 10 ms. **Material and Methods:** The study included 21 patient suffering from Parkinson's disease. After reviewing the medical records and analyzes the inclusion and exclusion criteria, patients were subjected to the same procedure examining auditory cognitive potentials (P300 wave) and the results were analyzed and compared to reference value for healthy population. **Results:** We have shown that patients with Parkinson's disease have prolonged P300 targeted and frequent stimulus latency compared to reference value for healthy population. From 21 patient 18 had a pathological P300 target stimulus amplitude, and even 20 patients had pathological P300 frequent stimulus amplitude. **Conclusion:** People with Parkinson's disease have altered P300 which indicates the presence of cognitive dysfunction in these patients.

Keywords: P300, auditory evoked potentials, Parkinson's disease, cognitive dysfunction.

1. INTRODUCTION

Parkinson's disease (PD) is chronic, progressive neurodegenerative disease of CNS caused by massive cell death in the dopamine-containing area called substantia nigra and locus ceruleus (1). The resulting dopamine deficiency in the basal ganglia leads to a movement disorder that is characterized by classical parkinsonian motor symptoms. The exact cause of PD is unknown but is believed to be associated with interaction of gene and environmental causes. PD can be divided in two groups: primary parkinsonism and secondary parkinsonism. Primary parkinsonism is due to classic idiopathic Parkinson's disease and includes loss of more than 80% of pigment-bearing neurons. Secondary parkinsonism could be due to many known causes such as loss of neurotransmitter dopamine, other neurodegenerative disorders, use of drugs or exposure to toxins, hydrocephalus, etc. (1, 2). The symptoms generally come on slowly over time and with different intensity. Early in the disease, the most obvious are tremor, rigidity and bradykinesia. It is usually a rest tremor; maximal at rest and disappearing with voluntary movement and sleep and feature of tremor is „pill-rolling". Rigidity is stiffness and resistance to limb movement caused by increased muscle tone and in PD is described like „lead-pipe rigidity" or „cogwheel rigidity". With rigidity development movements became slower (bradykinesia) which can cause muscle pain. Other recognized motor signs and symptoms include postural instability such as festination (rapid shuffling steps and a forward-flexed posture when walking), speech and swallowing disturbances including voice disorders, mask-like face expression or small handwriting (2, 3, 4, 5). Although the range of possible

motor problems that can appear is large, PD can cause neuropsychiatric disturbances known as „non-motor symptoms" which can range from mild to severe (6). This includes disorders of mood, cognition, behavior, and thought. Symptoms can manifest with depression, anxiety, hallucinations or delusions. Alterations in the autonomic nervous system can lead to orthostatic hypotension, urinary incontinence, constipation and food aspiration caused by swallowing difficulties (3, 7, 8, 9). There is no lab test that will clearly identify the disease so medical history and history play an important role (10, 11). To estimate the severity and progression of disease different type of scales are used, such as Hoen and Yahr Staging of PD and UPDRS (12). There are also brain scans which are used to rule out disorders that could give rise to similar symptoms (3, 13). Cognitive electrophysiology plays an important role because it is not limited by existence of a physical disability (14, 15). There is no cure for PD, but medications, surgery, and physical therapy can provide relief from the symptoms. Levodopa is drug which is used as first choice for treatment of motor symptoms. In surgical treatment, apomorphine and duodopa pump are more often used (16). Although PD is mostly presented with motor symptoms, cognitive disorders as dementia play very important role (17). Risk of developing dementia is 2-6 times bigger in patients with PD and increases with the duration of illness (18). Other symptoms like hallucinations or delusions are also present and they are believed to be repercussion of subcortical pathology (19, 20, 21). Therefore cognitive disorders can be assessed by neuropsychological tests such as Mini-Mental State Examination (MMSE) which is used as screening test. There are also some other tests like Trail Making Test (TMT), Rev Auditory Verbal Learning Test (RAVLT), Wisconsin Card Sorting Test categories (WCTS), Hooper Visual Organization Test (HVOT) (22). Montreal Cognitive Assessment (MoCA) is also very good screening test but they all depend on patient compliance which is their main limitation (23). In these cases, cognitive electrophysiology plays an important role because it is not limited by existence of a physical disability. In most of the studies were used auditory, and in some visual cognitive evoked potentials, so we can distinguish visual P300 and auditory P300 (24, 25). The P300 is an endogenous potential, which belongs to the event-related potential, which express the electrical activity of the brain associated with anticipation of the stimulus, decision making and control of behavior (26). The P300 is elicited by a discrimination task, the oddball paradigm, which consists of a series of frequent (untargeted) and target stimuli, randomly administered in the proportion of 4:1 respectively. The subject's task is to evaluate the occurrence of the significant stimulus, the target one, engaging expectancy, attention and memory during the performance. The subject has to ignore frequent stimuli and has to inhibit the tendency to respond to them. The task includes switching attention to target stimuli and distraction them from frequent stimuli (27, 28). The result of these tasks is the P300 wave. Latency and amplitude, describing wave P300, are used as neuropsychological indicators of cognitive impairment in a lot of diseases and conditions like migraine because of its objectivity and noninvasive. P300 is particularly important in the assessment of cognitive disorders in the early stages of PD, when cognitive changes are more subtle than in the later stages of the disease (28, 29).

2. MATERIAL AND METHODS

The study included 21 patient suffering from Parkinson's disease. The inclusion criteria was exclusively diagnosed Parkinson's disease. Participants gave their consent to participate in research. After reviewing the medical records and analysis of inclusion and exclusion criteria, patients were subjected to the procedure testing auditory cognitive potentials (P300). The examination was conducted on the device Medelec Synergy-Oxford Instruments (San Francisco, USA). Recording P300 was carried out according to standard procedure (30). The potentials were recorded using Ag /AgCl surface electrodes placed according to the international 10-20 system at the point Fz, Cz, Pz, C3, C4 and mastoid (31). Electrodes were placed on the previously well cleansed skin of scalp, attached by contact paste and fixed by peace of cotton. The value of the electrode impedance was checked prior to use and maintained below 5 kΩ. Patients were placed on a bed in a darkened, quiet room. At the beginning of the recording, the examiner explained the process and to the each patient was determined hearing threshold. For conducting the tests we used sound stimuli intensity 70 dB above the hearing threshold. The patient listened stimuli through headphones. The ratio of target and frequent stimuli was 1:4, as per standard. The patient was asked to count rare, target stimuli. We worked two consecutive, equal records to each respondent to assess the reproducibility and depletion of neurons. From each patient we took date about age, sex, disease duration and the type of the disease. Information gathered during the history was confirmed by neurologists. After the examination, we estimated the length of P300 targeted and frequent stimulus latency, what is processing time of auditory stimulus, and P300 targeted and frequent stimulus amplitude and we compared them with reference interval for healthy population. The P300 targeted/frequent stimulus latency expressed numerically with reference value 300 ± 10 ms, and the P300 targeted/frequent stimulus amplitude expressed as normal, lower, low and very low.

All data were analyzed using the statistical package Statistica 7.0 (StatSoft, Inc., Tulsa, USA). Quantitative variables were tested using the Mann-Whitney test. Regarding the qualitative data, the results were classified into normal and abnormal and further classified into types of abnormalities. The Fisher Exact Test was used for the statistical analysis of the qualitative data. For analysis of correlation between age and disease duration with changes in the P300 target/frequent stimulus amplitude and latency Spearman's rank correlation coefficient was evaluated. All tests were carried out with a statistical significance of 95% ($p < 0.05$).

3. RESULTS

The study group included 21 patient suffering from Parkinson's disease with normal neurological development without any other neurological disorder. Participants were referred by a neurologist and their results were compared with reference interval for healthy population. From 21 patient 12 (57%) were male and 9 (43%) female, age ranged from 65 to 82 years with a median of 70.38 years (Table 1).

		Patients with Parkinson's disease
Age (years)		70.38 (65-82)
Gender	Male	12 (57)
	Female	9 (43)

Review of median (min – max) age i number (%) of patients.

Table 1. Demographic characteristics of patients with Parkinson's disease.

We demonstrate a statistically significant difference in the median length of the P300 wave latency of target stimulus between group of patients with Parkinson's disease compared to reference value for healthy population. The median length of the P300 wave latency of target stimulus in patients with Parkinson's disease was 314.76 ms (299-326) until as the reference value for healthy population was taken value of 300± 10 ms. We have also shown that there is a statistically significant difference of the median length of the P300 wave latency of frequent stimulus. The median length of the P300 wave latency of frequent stimulus in patients with Parkinson's disease was 345 ms (319-353) and reference value for healthy population was 300± 10 ms just like one in the P300 wave latency of target stimulus (Table 2).

By analyzing the P300 wave amplitude of target stimulus in the group of patients suffering from Parkinson's disease of 21 patient, 18 had abnormal findings. Regarding the P300 wave amplitude of frequent stimulus, of 21 patient, 20 of them had abnormal findings (Table 3).

	Patients with Parkinson's disease	Reference interval	P
P3t00 terget stimulus latency (ms)	314.76 (299-326)	300± 10	0.473*
P300 frequent stimulus latency (ms)	345 (319-353)	300± 10	<0.001*

*Mann Whitney test.

Table 2. Review of median (min – max) of P300 target stimulus latency and P300 frequent stimulus latency in patients with Parkinson's disease compared to reference interval for healthy population.

		Patients with Parkinson's disease
P300 target stimulus amplitude	Normal	3
	Lower	6
	Low	8
	Very low	4
P300 frequent stimulus amplitude	Normal	1
	Lower	2
	Low	4
	Very low	14

* Fisher's exact test.

Table 3. Review of P300 target and frequent stimulus amplitude in patients with Parkinson's disease.

	Age (years)	Disease duration (years)
P300 target stimulus amplitude	0.198 (P=0.390)	0.034 (P=0.883)
P300 frequent stimulus amplitude	-0.414 (P=0.062)	0.019 (P=0.936)
P300 target stimulus latency	-0.057 (P=0.806)	0.263 (P=0.249)
P300 frequent stimulus latency	0.281 (P=0.217)	0.627 (P=0.002)

Table 4. Review of Spearman's rank correlation coefficient (ρ) (P) of the investigated variables with age and disease duration.

From the analysis of the correlation coefficient of the investigated variables with age and disease duration we get that there is a statistically significant negative correlation between P300 frequent stimulus amplitude and patients age. There is also a statistically significant positive correlation between P300 frequent stimulus latency and disease duration (Table 4).

4. DISCUSSION

In our study we have shown that patients with PD have prolonged P300 target and frequent stimulus latency. From 21 patients 18 had pathological P300 target stimulus amplitude, and 20 had pathological P300 frequent stimulus amplitude. All participants from research group had abnormal findings at least one parameter that describes the P300, or amplitude and/or latency of the P300.

The findings of this research have been confirmed and described in studies Matsui et al. (32), Solís-Vivanco et al. (15), Koberskaia et al. (33), Raudino et al. (34), Philipova et al. (35), Jiang et al. (36). They all show that patients with PD have changes in some parameter that describes the P300 which suggests that cognitive dysfunction is one of most common symptoms of PD .

Our study has also shown that there is connection between the P300 targeted/frequent stimulus amplitude and latency with patient age and disease duration. We get that there is a statistically significant negative correlation between P300 frequent stimulus amplitude and patients age and that there is also a statistically significant positive correlation between P300 frequent stimulus latency and disease duration. These findings can be explained by the fact that the disease in individual patients occurred for the first time at different ages. Previous studies also have shown a shortening of the P300 latency during aging, but no clear evidence the effect of age on the amplitude of the P300 (37).

So two major neurophysiological markers of cognitive function are latency and amplitude. Latency is a reliable indicator of the speed of information processing in the brain. Prolonged latency presents prolonged information processing time. On the other hand, reduced of the amplitude reflected disruption in the activities of some centers like frontal and parietal cortex, thalamus and temporomesial cortex or temporal dispersion of information processing. For the diagnosis of cognitive dys-

function pathological only one of the parameters is sufficient or prolonged P300 latency and/or reduced P300 amplitude. In correlation with the above facts, we can conclude that people with PD have altered the P300. Evidence of these changes indicates that patients with PD have frequent cognitive dysfunctions. That's why these markers are so important. Not only like one of the earliest signs of cognitive dysfunctions but they are also important in process of planing rehabilitation measures and physical therapy. The procedure is very simple and noninvasive which also gives them priority in diagnosing and recognizing symptoms in early phase.

5. CONCLUSIONS

We found that patients suffering from PD have prolonged P300 target and frequent stimulus latency, and have a reduced P300 target and frequent stimulus amplitude.

Based on the obtained results that show frequent incidence of P300 changes in the patients with PD, which indicates the presence of cognitive dysfunction in these people, early diagnosis of cognitive impairment should be mandatory for the planning of additional supportive treatment. In this regard, estimates of latency and amplitude of P300 can be a valuable support for clinicians in the objectification of cognitive dysfunction due to the simplicity and noninvasive of procedure.

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