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Research / Araştırma

Evaluation of Cognitive Functions in Parkinson's Patients without Dementia with Auditory Event Related Potential (P300)

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ABSTRACT

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Objective: Idiopathic Parkinson's disease is a clinical situation characterized by akinesia, rigidity, and tremor, and results from the degeneration of the dopaminergic nervous system. As the disease progresses over time, depression, cognitive dysfunction and alterations in cognitive functions are added to the movement disorder at varying rates. The P300 component is a useful parameter for cognitive processing studies on PD patients, as it is independent from motor skills. The current study aimed to show the effects of the PD on the cognitive functions by evaluating the cognitive functions of IPD patients without dementia with the help of an event related potential component, P300 test.

Methods: Thirty-eight patients (25 males and 13 females), ranging in age between 40 and 80 years (mean: 58.8 years), were included to the study and the control group consisted of 39 volunteers (25 males and 14 females), ranging in age between 44 and 84 years (mean: 63.5 years), who did not have a history of cerebrovascular disease, dementia, or depression. The participants were informed about the content and the practice of the study, and informed consent forms were obtained. Neurological examination, standardized mini mental test, Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr Scale, Hamilton Depression Rating Scale (HAM-D), and P300 tests were performed on the patients. Standardized mini mental test (SMMT), HAM-D, and P300 tests were performed in the control group.

Results: P300 latencies in Parkinson's patients were significantly prolonged compared to the control group. There was a decrease in P300 amplitude values with increasing HAM-D.

Conclusion: P300 latency reflects the rate of stimuli classification by mental process, attention, and cognitive processing. Even if no dementia is present in PD patients, there is a dysfunction in these functions, and it can be demonstrated by the P300 test, which is independent from motor skills.

Key words: Cognitive functions, idiopathic Parkinson's disease, P300-event related potentials

ÖZET

Demansı olmayan Parkinson hastalarında işitsel olaya bağlı potansiyel (P300) ile kognitif fonksiyonların değerlendirilmesi

Amaç: İdiyopatik Parkinson hastalığı, dopaminerjik sinir sistemi dejenerasyonuna bağlı olarak gelişen akinezi, rijidite ve tremor ile karakterize bir tablodur. Hareket bozukluğuna zaman içerisinde hastalığın ilerlemesi ile birlikte depresyon, kognitif fonksiyon bozukluğu ve bilişsel fonksiyonlarda etkilenme değişen oranlarda eklenir. P300 bileşeni Parkinson hastalığında bilişsel işleme çalışmaları için yararlı bir parametredir, çünkü motor becerilerden bağımsızdır. Bu çalışmada demansı olmayan idiyopatik Parkinson hastalarının kognitif işlevlerini olaya ilişkin uyarılmış potansiyellerden P300 testi ile değerlendirerek, Parkinson hastalığının kognitif fonksiyonlar üzerine etkisini göstermeyi amaçladık.

Yöntem: Yaşları 40 ile 80 arasında değişen (ortalama 58.8) 25 erkek ve 13 kadın olmak üzere toplam 38 hasta ve kontrol grubu olarak da serebrovasküler hastalık öyküsü, demans ve depresyonu olmayan, yaşları 44 ile 84 arasında değişen (ortalama 63.5) 25 erkek ve 14 kadın olmak üzere toplam 39 gönüllü çalışmaya alındı. Katılımcılara çalışmanın içeriği, uygulanışı ile ilgili bilgi verildi ve onam formu alındı. Hastalara, nörolojik muayene, Standardize Mini Mental Test, Birleşik Parkinson Hastalığı Derecelendirme Ölçeği (UPDRS), Hoehn ve Yahr Ölçeği, Hamilton Depresyon Ölçeği (HDÖ) ve P300 testleri uygulandı. Kontrol grubuna Standardize Mini Mental Test, HDÖ ve P300 testleri uygulandı.

Bulgular: Parkinson hastalarının P300 latansları, kontrol grubuna göre anlamlı düzeyde daha uzundu. Parkinson hastalarında HDÖ puanları arttıkça P300 amplitüd değerlerinde azalma görülmekteydi.

Sonuç: P300 latansı, mental sürecin stimulus sınıflama hızını, dikkat ve zihinsel işlemeyi yansıtır. Parkinson hastalarında demans olmasa da bu işlevlerde bir bozukluk vardır ve bu da motor becerilerden bağımsız bir test olan P300 testi ile gösterilebilir.

Anahtar kelimeler: Bilişsel işlevler, idiyopatik Parkinson hastalığı, P300-olay ilişkili potansiyeller

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INTRODUCTION

Idiopathic Parkinson's disease (IPD) is a common proteinopathy that is caused by the misfolding of alpha-synuclein, and it is the most frequent neurodegenerative movement disorder in early ages (1,2). When describing the major clinical features of the disease, James Parkinson stated six fundamental features: tremors at rest, rigidity, bradykinesia-hypokinesia, flexion posture, loss of postural reflexes, and freezing phenomenon. The degeneration of nigral dopaminergic neurons, which ends in striatal dopaminergic deficit, is the fundamental neurochemical deficit in IPD. The underlying reason for the cognitive dysfunction in most IPD patients is the interruption of the striato-pallido-thalamic-dorsolateral-frontal connections. Akinesia, a motor symptom of IPD, shows the strongest association with dopamine depletion and mental disorders. Therefore, it is suggested that cognitive dysfunction in IPD results from the same subcortical lesion causing motor symptoms (nigrostriatal dopaminergic system lesion) (3).

Electrical changes that are generated in the brain in response to a stimuli or an event, and which are recorded on the scalp, are called event-related potentials (ERP). The wave form of ERPs shows a large positive component to this stimulus, and is generally referred to as the P300 complex. P300 is among the most investigated of the ERPs, and is the greatest endogenous ERP component that is easily processed. Recently, researchers have begun to accept the P300 potential as the neurophysiological index of cognitive functions. P300 reflects cognitive decision making, attention, distinguishing stimuli, comparing their content with memory prints, and their classification (2). The changes in P300 amplitude reflect the degree or the quality of information process; latency, on the other hand, is related to cognitive ability and memory capacity (1). P300 is considered an electrophysiological indicator of neural events that are associated with cognitive functions, and is being used together with neuropsychiatric tests to evaluate cognitive functions. Studies have described two components of P300 (P300a and P300b), and late P300 wave (P300b) is considered to reflect the detection of voluntary stimuli and is associated with working memory (4).

The present study aimed to compare decision making, attention, keeping attention, distinguishing stimulus, and the memory prints of the stimulus between IPD patients and the control group by using the P300 test, which is independent from motor skills.

METHOD

Patients who were admitted to the neurology polyclinic at the Ankara Diskapi Yildirim Beyazit Training and Research Hospital, who were recently diagnosed (minimum) or who were diagnosed with Parkinson's disease (PD) and were being followed-up for 19 years (maximum), who did not have dementia and depression were included in the study. Neurological examination, standardized mini mental test, Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr Scale, Hamilton Depression Scale (HAM-D), and P300 tests were performed on PD patients. Volunteers with similar age and demographic features were enrolled in the control group, and standardized mini mental test, HAM-D and P300 tests were performed. ERP studies on all participants were carried out in the Electrophysiology Laboratory at Ankara Diskapi Yildirim Beyazit Training and Research Hospital. Participants were informed about the content and the practice of the study, and written informed consent was obtained from each participant. Before the recording procedure, the participants were informed about the recording, and personal information (name, age, gender, hand preference, date of recording) were recorded. All P300 recordings were performed in a quiet environment in the electromyography (EMG) laboratory by using 2-channel EMG/UP instrument (Dantec Keypoint). Scalp needle electrodes were used. When the patients were in the supine position, the active electrode was placed at Cz, and the reference electrode was placed on the right mastoid. The electrode impedances were set below 5 ohm. The stimulus was set up to last for 1000 ms, having a frequency of 1 Hz, amplification of 50 mv/unit, and an analysis period of 100 ms/unit. The standard oddball paradigm was used as the stimulus method, and the objective was to distinguish rare sounds with a thin tone (2 kHz) that appeared with a 20% frequency among repetitive, thick tones (1 kHz), which had an 80%

frequency. Eighty dB was added to the hearing threshold, and the resulting stimulus was given regularly to both ears every 2 seconds. Rare repetitive stimuli were randomly distributed among the frequent stimuli. Patients were asked to count the number of rare stimuli. The Cz point was set as the active recording point to evaluate both latencies and amplitudes. At the end of recording, patients were asked about the number of target stimuli, and their responses were noted. The latency and amplitude of P300 were determined in the obtained trace.

Statistical Analyses

SPSS for Windows 11.5 software was used for data analysis. The Shapiro-Wilk test was used to determine the fitness of continuous variables to normal distribution. The descriptive statistics included mean±standard deviation or median (min-max) for continuous variables, and the number of cases and percentage (%) for categorical variables. The significance of median values between the groups was assessed by using the Mann-Whitney U-test when the number of independent groups was two, and by using the Kruskal-Wallis test when the number of independent groups was higher than two. Spearman's correlation test was used to evaluate the significance of the correlation between continuous variables. P values <0.05 were considered statistically significant.

RESULTS

Thirty-eight patients (25 males and 13 females), ranging in age between 40 and 80 years (mean: 58.8 years), were included in the PD patient group. Thirty-nine volunteers (25 males and 14 females) ranging between 44 and 84 years (mean: 63.5 years) were included in the control group. The mean education level was 5.14 years in the PD patients, and 6.12 years in the control group. There was no significant difference in P300 amplitude and latency levels between PD patients who received levadopa, dopamine agonists, MAO inhibitors, and anticholinergics at varying doses, combined, or as monotherapy, and patients who did not receive these treatments (Table 1). There were no significant differences in age and education level between the patients and the control group. In both groups, there was no significant correlation between the education levels and P300 amplitude and latency values (Table 2). The mean PD duration was 5.84 years, and the mean treatment duration was 5.29 years. There were no significant differences in PD duration and P300 amplitude (p=0.899) and latency (p=0.339). The localization of disease onset was the right side in 24 patients (63.2%), and the left side in 14 patients (36.8%). There was no significant correlation between the disease onset localization and P300 amplitude and latency values (Table 3). Regarding disease findings, when

Table 1: The association between anti-Parkinson treatments and P300 latency and amplitudes in PD patients

Variables	P300 Latency median (min.-max.)	p	P300 Amplitudes median (min.-max.)	p
Dopamine agonist		0.841		0.319
Do not use	440.0 (337.0-664.0)		4.5 (0.2-19.1)	
≤1.5 mg	445.5 (312.0-867.0)		5.1 (3.2-9.3)	
>1.5 mg	532.0 (338.0-740.0)		6.2 (3.9-15.3)	
Levodopa		0.119		0.517
Do not use	587.0 (402.0-867.0)		5.1 (4.5-8.9)	
≤300 mg	400.0 (337.0-650.0)		8.4 (0.2-19.1)	
400-600 mg	546.0 (312.0-664.0)		5.6 (0.5-9.2)	
>600 mg	461.0 (346.0-650.0)		4.7 (3.2-8.7)	
MAO Inhibitor		0.715		0.544
Do not use	499.0 (312.0-867.0)		5.0 (0.2-19.1)	
Use	441.0 (346.0-664.0)		6.6 (0.7-14.7)	
Anticholinergic		0.765		0.235
Do not use	448.0 (337.0-867.0)		6.1 (0.2-19.1)	
Use	572.5 (312.0-650.0)		4.9 (3.2-6.2)	

min: minimum, max: maximum

Table 2: Comparison of age, gender, P300 latency and amplitude between PD patients and controls

Variables	Control group (n=39)	Case group (n=38)	p
Age [Mean±sd (min-max)]	58.8±10.5 (44-84)	63.5±11.0 (40-80)	0.061
Sex [n (%)]			0.877
Female	14 (35.9)	13 (34.2)	
Male	25 (64.1)	25 (65.8)	
P300 Latency [median (min-max)]	334.5 (246.0-423.0)	456.0 (312.0-867.0)	<0.001
P300 Amplitude [median (min-max)]	5.00 (3.10-15.80)	5.10 (0.25-19.10)	0.676

min: minimum, max: maximum

Table 3: The correlation between age, disease duration, treatment duration, MDDRD, GYA, motor examination, treatment complication, total UPDRS, Hoehn and Yahr Scale score, Hamilton Depression Rating Scale, and P300 amplitude and latency

Variables	P300 Latency		P300 Amplitude	
	r	p	r	p
Age	0.181	0.28	-0.375	0.038
Disease duration	-0.021	0.90	-0.181	0.330
Treatment duration	-0.038	0.82	-0.143	0.450
MSBMS	-0.208	0.21	-0.037	0.840
ADL	-0.158	0.34	-0.221	0.230
Motor examination	-0.107	0.52	-0.225	0.230
Complications of treatment	0.277	0.11	-0.079	0.690
Total of UPDRS	-0.096	0.57	-0.239	0.200
Hoenhn and Yahr Scale	-0.166	0.32	-0.177	0.340
Hamilton Depression Rating Scale	-0.192	0.25	-0.365	0.044

MSBMS: Mental Status, Behavior and Mental Status, ADL: Activities of Daily Living, UPDRS: Unified Parkinson's Disease Rating Scale

tremor, rigidity, postural instability, bradykinesia, and P300 latencies were individually evaluated, there was no significant difference between the P300 latencies.

P300 latencies in Parkinson's patients were significantly prolonged compared to the control group (p<0.001) (Table 2). There was no significant difference in mean P300 amplitudes between PD patients and the control group (p=0.676). A significant inverse correlation was found between age and P300 amplitude in PD patients (r=-0.375, p=0.038) (Table 3).

The mean UPDRS score for mental status, behavior, and mood was 1.97, the mean UPDRS score for daily life activities was 9.73, the mean UPDRS score for motor examination was 11.92, the mean UPDRS score for treatment complications was 2.20, and the mean total UPDRS score was 26. There was no significant difference in P300 latency and amplitude values between the UPDRS subgroups. The mean total Hoehn and Yahr Scale score was 1.86. There was no significant correlation between Hoehn and Yahr Scale scores and P300 amplitude (p=0.319) and latencies (p=0.341) (Table 3). There was no significant difference in HAM-D latency values between the groups. The mean HAM-D scale point was 7.64 in PD patients. P300 amplitudes decreased in PD patients and in patients who did not meet the depression diagnostic criteria, while having HAM-D scores that were close to the pathological values (r=-0.365, p=0.044) (Table 3).

The mean MMT score was 26.4 in PD patients, and 26.8 in the control group.

DISCUSSION

PD was previously considered only as a primary motor system disease, while in recent years, studies have shown that PD also affects sensory functions, perception, cognitive functions, sleep, and emotional functions (5,6). Studies aimed towards the cognitive functions of PD patients have pointed out the most determinant feature is the deterioration of executive functions, which are defined as regulating behaviors towards an objective, planning, and organization. In this context, functions including conceptualization, problem-solving, finding rules, planning, generalization, and structuring are deteriorated in PD patients, and patients have trouble ordering the components of an action (7).

Cognitive dysfunctions affecting attention/executive functions, memory, and visual-spatial functions are observed in PD patients, even in early and mild cases, and the mean incidence of cognitive dysfunction in the second year of PD is 36%. The incidence of cognitive dysfunction within 15 years after diagnosis is 84%. Intellectual and cognitive impairment are well-known features of PD patients. In 20-30% of the cases, the disease can progress to focal dementia depending on frontal lobe dysfunction or multi-focal dementia. The P300 component of ERPs is a useful parameter for cognitive processing studies in PD, as it is independent from motor skills (8,9). The latency of P300 reflects the rate of stimuli classification by the mental process, attention, and mental processing (10). The hippocampus, amygdala, and associated structures play a role in the formation of the normal P300 latency (11). The loss of dopamine in the mesolimbic dopaminergic system can be responsible for prolonged P300 latency in PD patients. In the present study, the mean PD duration was 5.84 years, and the mean treatment duration was 5.29 years. There was no significant correlation between the treatment duration and P300 latencies and amplitudes given the statistical information.

P300 studies on PD patients have shown that P300 latency is prolonged (6,12-16). Similar to the previous studies, we found that P300 latency was prolonged in PD patients compared to the control group (Table 2).

Disease duration, treatment duration, MDDRD, GYA, motor examination, treatment complications, UPDRS, and Hoehn and Yahr Scale were not significantly associated with P300 latencies and amplitudes (Table 3). Sohn et al. (17) carried out a study on 25 recently diagnosed PD patients and 20 controls, and found a reduction in P300 latency and motor symptoms under dopamine treatment, but were unable to find a significant correlation between these parameters. In the present study, there was no significant difference in P300 amplitude and latency levels between PD patients who received levadopa, dopamine agonists, MAO inhibitors, and anticholinergics at varying doses, combined, or as monotherapy, and patients who did not receive these treatments (Table 1). This, in turn, indicates that central dopaminergic mechanisms also play a role in the formation of P300 anomalies in PD patients. Prasher and Findley (6) carried out a study on 20 IPD patients and 20 controls, and found that reaction time was shorter after dopamine treatment; however, P300 latency was prolonged in IPD patients compared to healthy controls. These findings indicate a weak link between central cognitive functions and motor functions.

Depression is also a common symptom in Parkinson's patients. Kenangil et al. (18) carried out a study on 59 PD patients and 39 controls, and found a significant correlation between the depression frequency and disease severity. In a study by Agren et al. (19), the authors observed that patients with depression had significantly prolonged P300 latencies, together with a significant decrease in P300 amplitude compared to normal individuals. Kalayam et al. (20) reported that P300 amplitude decreases in depression. Considering that P300 reflects the cognitive functions associated with attention, anticipation, and the importance of the stimuli, this finding can be evaluated as the electrophysiological interpretation of cognitive dysfunction in patients with depression. Various studies investigating the effect of depression on induced potentials have reported that depression causes a reduction in P300 amplitude (21-25). Similar to these studies, in the present study there was a decrease in P300 amplitude values with increasing HAM-D scores ($p=0.04$) (Table 3).

In conclusion, the researchers of the current study observed a significant prolongation in P300 latency in Parkinson's patients compared to the control group. This finding revealed that whether dementia is present or not, prolonged P300 latencies, and dysfunctions in attention, stimuli classification rate, and cognitive processing are present in PD patients, and these dysfunctions could be detected with the P300 test, a test that is independent from motor skills. However, owing to the limitations of the current study and the differences in study design, detailed neuropsychological evaluations were not performed, and only cognitive functions were analyzed by using SMMT. Future studies are required to further investigate the association between cognitive functions of PD patients and P300.

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