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Diagnostic application of cognitive event-related potentials in Parkinson's disease

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Dijagnostička primena kognitivnih evociranih potencijala kod Parkinsonove bolesti

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ABSTRAKT

Idiopatska Parkinsonova bolest je hronični, progresivni, neurodegenerativni poremećaj od koga oboljeva svaka stota osoba u populaciji starijoj od 60 godina. Osim dobro poznatih motornih znakova bolesti (bradikinezija, rigiditet i tremor), u kasnijim fazama, dolazi do razvoja kognitivnih poremećaja i do ispoljavanja pune kliničke slike demencije. Značajan preduslov adekvatnog kognitivnog funkcionisanja je očuvana pažnja. Rano prepoznavanje kognitivnih poremećaja je vrlo značajno, ne samo zbog medicinskih razloga već i zbog mogućih socijalnih problema.

Cilj rada je utvrđivanje dijagnostičkog značaja kognitivnih evociranih potencijala za otkrivanje poremećaja pažnje u različitim stadijumima Parkinsonove bolesti.

Primenom neurofiziološke metode kognitivnih evociranih potencijala ispitano je 45 pacijenata oba pola obolelih od idiopatske Parkinsonove bolesti, starosti od 55 do 76 godina.

Iako su sve registrovane latence u našoj studiji bile u okvirima fizioloških vrednosti, postoji statistički značajna razlika srednjih vrednosti latenca talasa N2 i P3 izmedju kontrolnih subjekata i parkinsonih bolesnika. Bez obzira što parkinsoni bolesnici nemaju jasne kliničke znake demencije, kod njih svesno prepoznavanje nastale promene u nizu stimulusa traje duže u odnosu na zdrave subjekte kontrolne grupe.

Na osnovu dosadašnjih rezultata može se zaključiti da navedene komponente kognitivnih evociranih potencijala, naročito P3 talas, mogu biti korisno dijagnostičko sredstvo u validaciji kognitivnih poremećaja kod nedementnih parkinsonih bolesnika.

KLJUČNE REČI

Parkinsonova bolest, kognitivni evocirani potencijali, talas P3, pažnja.

Diagnostic application of cognitive event-related potentials in Parkinson's disease

ABSTRACT

Idiopathic Parkinson's disease is a chronic, progressive, neurodegenerative disorder that affects every hundredth person in the population over the age of 60. In addition to the well-known motor signs of the disease (bradykinesia, rigidity and tremor), in the later stages, there is the development of cognitive disorders and the manifestation of the full clinical picture of dementia. An important prerequisite for adequate cognitive functioning is preserved attention. Early recognition of cognitive disorders is very important, not only for medical reasons but also for possible social problems.

The aim of the work is to determine the diagnostic significance of cognitive event-related potentials (ERPs) for the detection of attention disorders in different stages of Parkinson's disease.

Using the neurophysiological method of cognitive ERPs, 45 patients of both sexes suffering from idiopathic Parkinson's disease, aged from 55 to 76 years, were examined.

Although all registered latencies in our study were within physiological values, there is a statistically significant difference in the mean latency values of the N2 and P3 waves between control subjects and parkinsonian patients. Regardless of the fact that parkinsonian patients do not have clear clinical signs of dementia, their conscious recognition of the resulting change in a series of stimuli takes longer compared to healthy subjects of the control group.

Based on the results so far, it can be concluded that the mentioned components of ERPs, especially the P3 wave, can be a useful diagnostic tool in the validation of cognitive disorders in non-demented parkinsonian patients.

KEY WORDS: Parkinson's disease, cognitive event-related potentials (ERPs), P3 wave, attention.

INTRODUCTION

Idiopathic Parkinson's disease is a chronic, progressive, neurodegenerative disorder that affects every hundredth person in the population over 60 years old. The prevalence of the disease in Europe and the USA varies from 60-187/100,000 in the general population, while the incidence is 10.1-24/100,000. The pathophysiological basis of the disease is the degeneration of the nigrostriatal dopaminergic neurotransmitter system, with a decrease in the level of dopamine in the striatum. In addition to dopaminergic, other neurotransmitter systems in the central nervous system are also affected - noradrenergic, serotonergic, cholinergic, GABA-ergic systems. The basic clinical signs, on the basis of which the diagnosis of the disease is made, are bradykinesia, rigidity and tremor, which are joined by postural disorders in the later stages of the disease. Until now, there are no other differential diagnostic procedures, e.g. laboratory or imaging methods, which can confirm the diagnosis of this disease.

In addition to the mentioned motor signs of the disease, in the later stages, there is the development of cognitive disorders and the manifestation of the full clinical picture of dementia. Early recognition of cognitive disorders is very important, not only for medical reasons but also for possible social problems. A prerequisite for cognitive functioning is preserved attention, whose disturbances lead the patient to the further development of cognitive insufficiency. Cognitive event-related potentials (ERPs) with the P3 wave are a very important instrument for examining these disorders.

AIM

The aim of the work is to determine the diagnostic significance of cognitive ERPs for the detection of attention disorders in different stages of Parkinson's disease.

METHOD

45 patients of both sexes suffering from idiopathic Parkinson's disease, aged from 55 to 76 years, were examined. According to the severity of clinical symptoms and signs, patients were classified into stages I-III according to the scale of Hoehn and Yahr. The control group consisted of 35 subjects of the same gender and age.

All patients were taking regularly prescribed antiparkinsonian therapy consisting of dopamine receptor agonists and levodopa, and during cognitive ERPs testing, all were in the "on" phase.

The registration of auditory cognitive ERPs was performed using the standard "oddball" paradigm, which is a task that requires the attention and concentration of the subjects. ERPs are detected by disc silver electrodes attached to the head. Registration was performed over the central, parietal, and temporal regions of the cortex. Two tones of 1000 and 2000 Hz, 80dB, were used as stimuli. The subject counted the target stimulus, i.e. higher 2000Hz tones, and ignored the standard 1000Hz tones. The stimulation rate was 1 stimulus in 2 seconds. The analysis time is 1000ms, the frequency range is from 0.1 to 50HZ,

and 32 target stimuli are averaged.[1]

The neuropsychological examination was performed using the Mini Mental State Examination (MMSE) test.

Statistical processing of the obtained latency values was performed using the standard t-test.

RESULTS

The structure of PD patients according to age and gender is shown in table 1. and chart 1. The study included patients who did not have signs of dementia, which was determined using the MMSE test.

STADIUM PB	MALE		FEMALE	
	Nr.	%	Nr.	%
I STADIUM	10	22.22	8	17.78
II STADIUM	11	24.44	6	13.33
III STADIUM	7	15.56	3	6.67
TOTAL	28	62.22	17	37.78

Table 1. Presentation of PD patients by stage and gender

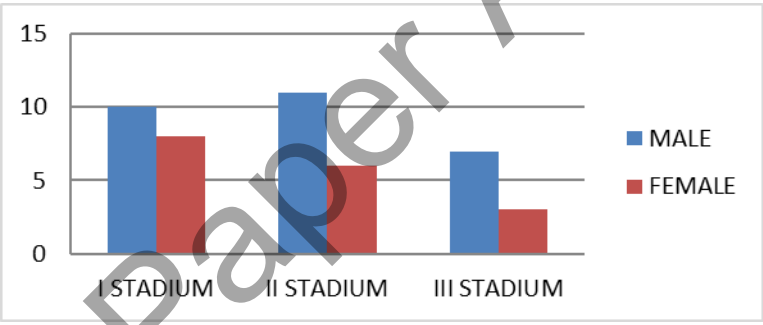

Chart 1. Presentation of PD patients by stage and gender

Statistically processed latencies parameters of registered ERPs - waves N1, P2, N2 and P3 are shown in table 2. and chart 2.

LATENCY (ms)	PD patients					CONTROL GROUP					Te
	X1	SD1	CV1	MIN1	MAX1	X2	SD2	CV2	MIN2	MAX2	
N1	103	9.2	0.1	85	128	98.2	7.4	0.04	82	110	1.74
P2	180	14.1	0.1	164	195	174	7.6	0.06	158	186	1.96
N2	262	22.8	0.2	218	294	244	23.1	0.08	202	268	2.18
P3	361	27.4	0.2	312	410	342	26.5	0.04	304	362	2.42

X -middle value

SD -standard deviation

CV -coeffcient of variation

MIN -minimum value

MAX -maximum value

Te -empirical value of the t-test

Table 2. Presentation of the latencies of cognitive evoked potentials in the PD patient group and the control group

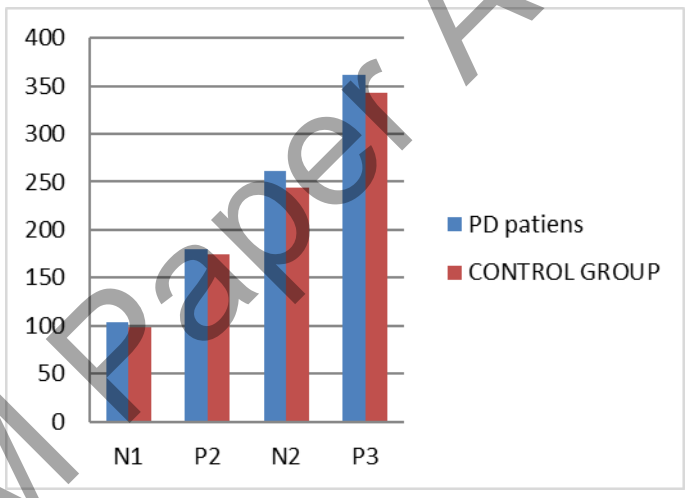

Chart 2. Presentation of the latencies (ms) of cognitive evoked potentials in the PD patient group and the control group

During the examination, the mean values of the latency of the N1 wave in parkinsonian patients were 103.1ms, while in healthy control subjects it was 98.2ms. The mean value of the P2 wave is 180.3 ms in parkinsonian patients, and 174.2 ms in healthy individuals. The mean latency of the N2 wave is 261.8ms in parkinson patients and 244.2ms in the group of healthy individuals. The mean latency of the P3 wave is 361.4ms in parkinsonian patients and 342.2ms in healthy individuals of the control group.

DISCUSSION

Selective attention refers to the capacity to focus on individual stimuli in the presence of distracting influences from other, external or internal stimuli. Attentional mobility includes the capacity to switch from one stimulus to another. Concentration corresponds to maintaining attention on a certain type of activity. Distractedness and inattention are symptoms of disorders of the mechanisms involved in the organization of attention.

In non-demented parkinsonian patients, there may be relatively isolated or combined disorders of executive, visuospatial and memory functions. Such disorders can also be detected in patients who have preserved their professional competence and do not necessarily evolve to the clinical picture of dementia. A risk factor for the onset of dementia can be considered low achievement on the verbal fluency test as well as depression.

Hypofunction of the dopaminergic (primarily in the mesocorticolimbic tract), cholinergic and other neurotransmitter systems is significant in the pathophysiological basis of the described neuropsychological disorders.[2]

Auditory cognitive ERPs are thought to be a very good indicator of mental function, as they are highly dependent on cognitive skills, including attention and discrimination. Its application is an effective assessment tool in patients with PD due to its good correlation with other neurocognitive tests that measure key features of the disease.[3]

During the recording of the auditory cognitive ERPs, two wave complexes are registered. The first complex is an exogenous long-latency evoked potential that is generated in the primary auditory cortex and is a response to standard stimuli that the subject does not pay attention to. It is represented by a negative N1 and a positive P2 wave. Answers identical to this complex are obtained during registration that does not require conscious and voluntary activity. The N1 wave is the earliest response that can be modulated by psychological processes related to selective attention.

The second complex of waves marked as negative N2 and positive P3 has a more complex structure and is composed of components corresponding to the standard response as well as primarily endogenous components. During the registration of responses to target stimuli, the dominant record is the P3 wave, whose latency correlates with the speed of cognitive processes.

Lei et al. think that rhythmic auditory stimulation may compensate dysfunctions of the basal ganglia, involved with intrinsic evaluation of temporal intervals and action initiation or continuation. In the cognitive domain, rhythmic auditory stimulation containing periodically presented tones facilitates young healthy participants' attention allocation to anticipated time points, indicated by better performance and larger P3 amplitudes to periodic compared to random stimuli.[4]

In the study conducted by Folmer et al., patients with PD showed significantly longer latencies of the P3 and N2 wave components, as well as a lower amplitude of the N2 wave. The latency and amplitude of the N2 component were significantly related to the age of the participants. N2 amplitude was correlated with results from the Rey Auditory Verbal Learning Test of cognitive ability. Latency of the P3 and amplitude of the N2 components were significantly correlated with results from the Spatial Release From Masking behavioral central auditory processing assessment. The mentioned authors believe that the N2 and P3 wave components recorded in this study represent disturbed neural processing in parkinsonian patients.[5]
Using auditory cognitive ERPs - P3 wave, Hunerli et al. examined functional brain changes in patients with PD without cognitive impairment and patients with PD and mild cognitive deficit. Lower amplitudes of P3 waves were registered in parkinsonian patients without cognitive deficit compared to healthy subjects of the control group. Patients with mild cognitive deficits had lower P3 wave amplitudes compared to patients without cognitive deficits and subjects of the control group. The authors in this study confirm that the amplitude of the P3 wave can be a useful marker for the detection of preclinical changes before the onset of cognitive deterioration in PD.[6]
As with other neurodegenerative diseases, the influence of age on the onset and progression of cognitive dysfunction has been investigated in PD. Using neuropsychological tests and auditory cognitive ERPs - P3 wave, Tang et al. examined patients with early and late onset PD. The results of this study show that although patients with early-onset PD had a longer disease duration, their cognitive dysfunction progressed more slowly. P3 wave latencies were significantly longer with lower P3 wave amplitudes in the group of patients with later onset of PD. The current findings showed that cognitive dysfunction progressed more slowly in the early-onset PD group. Although patients with later-onset PD showed shorter disease duration, their cognitive abilities, including executive function, visuospatial function, and attention, were impaired.[7]
Toda et al. investigated auditory cognitive ERPs - P3 wave in demented and non-demented patients with PD. There were no significant differences neither in the amplitude nor in the latency of the P3 wave between non-demented parkinsonian patients and healthy subjects of the control group. In demented patients with PD, the latency of the P3 wave was significantly prolonged compared to control subjects. These results suggest that demented parkinsonian patients have impairments in stimulus evaluation, response selection and execution.[8]
The aim of the research carried out by Tokic et al. was to show that patients with Parkinson's disease have a reduced amplitude and prolonged latency of the auditory cognitive ERPs - P3 wave. The testing procedure was conducted and the results were analyzed and compared with the reference value for a healthy population. The results showed that parkinsonian patients have a prolonged latency of the P3

wave, which confirms the presence of cognitive dysfunction in these patients.[9]

Impairment of cognitive functions significantly affects the quality of life of Parkinson's patients. Although numerous studies have shown that the amplitude and latency of the N2 and P3 waves are correlated with cognitive functions, there are also many controversial findings. Therefore, Xu et al. conducted a meta-analysis of research on N2 and P3 amplitude and latency in PD patients. They concluded that N2 and P3 waves may be potential electrophysiological biomarkers of early cognitive impairment in PD. Due to the simplicity and non-invasiveness of the procedure, they can be a significant support to clinicians in the diagnosis of early cognitive impairment in patients with PD.[10]

Yilmaz et al. investigated whether additional electrophysiological tests help in making a clinical diagnosis of mild cognitive impairment in Parkinson's disease. They assessed changes in the P3 component in non-demented PD patients and analyzed the correlation between cognitive characteristics and changes in the P3 component. In all non-demented patients with PD and in the control group, P3 latencies were within physiological limits, while in parkinsonian patients with mild cognitive deficits they were prolonged. The results of this study show that the P3 component represents a diagnostic tool in determining PD with a mild cognitive deficit.[11]

Changes in cognitive functions are an integral part of the clinical presentation of PD. Prabhakar et al. investigated changes in P3 waves in the early stages of PD and the effect of dopaminergic therapy. By applying auditory cognitive ERPs, they determined that the latency of the P3 wave was not significantly increased in the early stages of PD. This latency was reduced by the introduction of dopaminergic therapy, but later increased again. Further consideration of the implications of these data is needed.[12]

The conduction time of the depolarization wave within the primary auditory cortex reflects the latencies of the N1 and P2 components, which are correlates of sensory processes in the CNS. The latency of the N2 wave is a correlate of conscious recognition of a change in a series of given stimuli, and it is a reflection of early cognitive processes. The latency of the P3 wave corresponds to the stimulus evaluation time, and it represents the speed of stimulus classification based on the discrimination of two events.

Although all registered latencies in our study were within physiological values, there is a statistically significant difference in the mean latency values of the N2 and P3 waves between control subjects and parkinsonian patients. The mean values of the latencies of the N1 and P2 waves did not differ statistically significantly between these two groups of subjects.

CONCLUSION

Our study also confirmed the conclusion of previous research that the N2 and P3 components of cognitive auditory ERPs represent a neurophysiological correlate of global cognitive functioning. The

difference in the duration of stimulus evaluation between parkinsonian patients and healthy subjects implies that recognition of changes in a series of uniform stimuli takes longer in non-demented parkinsonian patients, which indicates possible incipient cognitive impairment. Regardless of the fact that parkinsonian patients do not have clear clinical signs of dementia, their conscious recognition of the resulting change in a series of stimuli takes longer compared to healthy subjects of the control group. Based on the results so far, it can be concluded that the mentioned components of auditory cognitive ERPs, especially the P3 wave, can be a useful diagnostic tool in the validation of cognitive disorders in non-demented parkinsonian patients.

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