P300 Wave Changes in Patients with Multiple Sclerosis

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Original paper
ABSTRACT
Introduction: In patients with multiple sclerosis among other symptoms occur cognitive dysfunctions, which can be shown by P300 wave changes. **Goal:** The aim of this study was to demonstrate that patients with multiple sclerosis have reduced amplitude and prolonged latency, longer than 300 ± 10 ms. Methods: The study included group of patients with multiple sclerosis and control group. After reviewing the medical records both groups of 14 participants were subjected to the same testing procedures auditory cognitive potentials (P300). **Results:** We have shown that patients with multiple sclerosis don't have prolonged P300 target stimulus latency, but they have a longer P300 frequent stimulus latency for 18 ms. From 14 patients seven had a pathological P300 target stimulus amplitude, and even 12 patient had pathological P300 frequent stimulus amplitude. **Conclusion:** People with multiple sclerosis have altered P300 which indicates the presence of cognitive dysfunction in these patients.
Key words: P300, auditory brain stem evoked potentials, multiple sclerosis, cognitive impairment.

1. INTRODUCTION

Multiple sclerosis (MS) is a progressive, inflammatory, demyelinating disease caused by the destruction of the myelin sheath by autoantibodies and immune cells (1). Because of the widespread development of the myelin destructions, MS results in a broad range of symptoms, which include motor, cognitive, and neuropsychiatric problems (2).

Cognitive impairment in MS is reported in 45% to 70% of patients occurring with specific patterns and varying prevalence estimates (3, 4, 5, 6). Mostly impaired cognitive domains are attention, information processing speed, recent memory and verbal fluency. Deficits of executive function, abstract reasoning and visuospatial abilities are less frequently reported in literature. Language seems to be relatively preserved in task of naming, comprehension, grammar and syntax (7, 8). Cognitive disorders are possibly due to subcortical pathology as is the case in the subcortical dementia associated with other chronic diseases (9).

Cognitive disorders can be assessed by neuropsychological tests, which, depending on patient compliance, can last 3-5 hours. The main limitation of neuropsychological testing in patients with MS is a physical disability, which includes the reduction of visual acuity and fine motor limit. On the other hand, preliminary screening tests, such as the Mini-Mental State Examination, proved to be insensitive to mild cognitive impairment. In these cases, cognitive electrophysiology plays an important role because it is not limited by existence of a physical disability (10, 11). In most of the studies were used auditory, and in some visual cognitive evoked potentials, so we can distinguish visual P300 and auditory P300 (12, 13, 14, 15).

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. The P300 is measurable brain response to certain visual or auditory stimuli. P indicates the position of the peak of the wave, i.e. the positive deflection of the curve, and numeral 300 indicates the latency of occurrence of wave after stimulus, with the highest amplitude over the central part of the parietal scalp. 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 (16, 17). 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 (18).

The result of these tasks is the P300 wave. Latency and amplitude, describing wave P300, are used as neuropsychological indicators of cognitive impairment in MS because of its objectivity and non-invasive. P300 is particularly important in the assessment of cognitive disorders in the early stages of MS, when cognitive changes are more subtle than in the later stages of the disease (19).

2. GOAL

The aim of this study was to demonstrate that patients with multiple sclerosis have statistically significant changes of P300. The changes of P300 are reduced amplitude and prolonged latency, longer than 300 ± 10 ms.

3. METHODS

Study population
The study was conducted at the Reference Centre for evoked potentials of Croatian Ministry of Health, Department of Neurology, University Hospital Split. Data were collected in the period from January 1st, 2012 until May 1st, 2013.

The study included two groups of 14 participants. The inclusion criteria for

the control group were history of normal neurological development, normal hearing thresholds, absence of psychiatric diagnoses, no complaints of tinnitus, and no auditory processing disorders. For the research group, the inclusion criteria were medical diagnosis of MS based on the criteria proposed by McDonald et al. (20), and normal hearing thresholds.

Participants gave their consent to participate in research. Ethics committee of University Hospital Split approved the implementation of the research and the use of medical records.

Recording auditory P300

After reviewing the medical records and analysis of inclusion and exclusion criteria, both groups were subjected to the same 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 (21). 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 (22). 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.

Date collection

From each patient we took date about age, sex, disease duration and the type of the disease. Information gathered during the anamnesis 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. 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.

Statistical analysis

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).

4. RESULTS

The two groups were composed by 14 participants each with 12 females and two males, age ranged from 12 to 64 years with a median of 44.5 years. Participants in the research group were referred by a neurologist. Participants in the control group were collected randomly from the outpatient population. Participants in the control group were age-and gender-matched to the research group participants.

We didn't demonstrate a statistically significant difference in the median of P300 target stimulus latency between patients with MS and the control group (Z = 0.717, P = 0.473) (Table 1).

Median of P300 frequent stimulus latency is longer in the group of patients with MS than in the control group for 18 ms (Z = 3.7, P < 0.001) (Table 1).

In the group of patients with MS of the 14 patients, 12 had abnormal P300 frequent stimulus amplitude. In control group only one had pathological amplitude while the rest were normal (Table 2).

In the group of patients with MS seven of them had normal findings P300 target stimulus amplitude, and seven pathological, whereas in the control group, 13 of them had normal findings (Fishers exact test: P = 0.016) (Table 3).

In the group type of the disease eight patients had relapsing-remitting multiple sclerosis, five had secondary progressive multiple sclerosis, and one had primary progressive multiple sclerosis. The median of disease duration was 9 years (min-max: 1-39 years).

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 target stimulus latency and patients age (Table 4).

5. DISCUSSION

In our study we have shown that patients with MS don't have prolonged P300 target stimulus latency, but have a longer P300 frequent stimulus latency for 18ms. From 14 patients seven had pathological P300 target stimulus am-

	Patients with multiple sclerosis	Control group	Statistical significance
P300 target stimulus latency (ms)	301 (292-318)	300.5 (295-306)	P=0.473*
P300 frequent stimulus latency (ms)	318 (295-361)	300 (293-305)	P<0.001*

Table 1. Review of median (min−max) of P300 target stimulus latency and P300 frequent stimulus latency compared to the test groups. *Mann Whitney test

P300 frequent stimulus amplitude	Patients with multiple sclerosis	Control group
Normal	2	13
Lower	3	1
Low	5	0
Very low	4	0

Table 2. Review of P300 frequent stimulus amplitude compared to the test groups. Fishers exact test

plitude, and 12 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 Schochat et al. (23), Magnano et al. (19), Gonzáles-Rosa et al. (24), Matas et al. (25). Magnano et al. (19) showed that P300 latencies were significantly increased more than 2 S.D. and also lower P300 amplitudes were found with respect to an age-matched control group.

Our study has also shown that there is no connection between the P300 targeted/ frequent stimulus amplitude and latency with patient age and disease duration, except that there is a negative correlation between P300 target stimulus latency and patient's age. 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 (17). The study Magnano et al. (19) no statistical correlations were found between latency and/or amplitude of P300 with disease duration.

The importance of evaluation of the P300 in patients with MS in diagnosis of cognitive dysfunction is shown in many studies (12, 13, 19, 26, 27). Giesser et al. (26) could demonstrate a high correlation between P300 latencies and cognitive functions typically impaired in MS such as visual and verbal memory and storage and retrieval strategies. In several other studies as well, the increase of P300 latency was significantly correlated with both the cognitive impairment and the degree of white matter involvement revealed by MRI (12, 13, 27).

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 (frontal and parietal cortex, thalamus and temporo-mesial cortex) or temporal dispersion of information processing. For the diagnosis of cognitive dysfunction pathological only one of the parameters is sufficient or prolonged P300 latency and/or reduced P300 amplitude (19). In correlation with the above facts, we can conclude, despite the statistically insignificant difference of P300 target stimulus latency between the two groups, but given the evidence of a statistically significant difference

P300 target stimulus amplitude	Patients with multiple sclerosis	Control group
Normal	7	13
Lower	3	1
Low	3	0
Very low	1	0

Table 3. Review of P300 target stimulus amplitude compared to the test groups. Fishers exact test

	Age (years)	Disease duration (years)
P300 target stimulus amplitude	0.382 (P=0.178)	0.214 (P=0.463)
P300 frequent stimulus amplitude	0.095 (P=0.747)	-0.397 (P=0.160)
P300 target stimulus latency	-0.638 (P=0.014)	-0.398 (P=0.158)
P300 frequent stimulus latency	-0.152 (P=0.604)	-0.003 (P=0.991)

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

of P300 target stimulus amplitude that people with MS have altered the P300. Evidence of these changes indicates that patients with MS have frequent cognitive dysfunctions.

6. CONCLUSION

We found that patients suffering from MS don't have prolonged P300 target stimulus latency, but have a reduced P300 target stimulus amplitude, and prolonged P300 frequent stimulus latency and reduced P300 frequent amplitude.

Based on the obtained results that show frequent incidence of P300 changes in the patients with MS, 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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