

# EVENT-RELATED POTENTIALS AND PACED AUDITORY SERIAL ADDITION TEST (PASAT) EVALUATION IN BEHÇET'S SYNDROME WITH SUBCLINICAL NEURAL INVOLVEMENT

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## ABSTRACT

• **Objective:** Behçet's Syndrome (BS), an inflammatory disorder, may affect central nervous system. A subclinical involvement, mainly affecting cognitive functions, might be observed in patients with BS. The aim of this study was to investigate this subclinical involvement.

• **Material and Method:** Event-related potentials (P300) and Paced Auditory Serial Addition Test (PASAT) were used. Patients with BS with normal MRI (BS), patients with neuro-BS and healthy subjects were enrolled to this study. Both BS and neuro-BS patients consisted of 14 patients (8 men and 6 women, mean age 35.9±8.2; 9 men and 5 women, mean age 36.7±8.3 respectively). There were 12 healthy subjects (8 men and 4 women, mean age 32.2±5.3) in control group.

• **Results:** P300 latencies obtained from central and frontal region were significantly longer for BS ( $p=0.006$ ,  $p=0.039$ ) and neuro-BS ( $p=0.019$ ,  $p=0.026$ ) groups

compared to controls. The latency on parietal region was significantly longer in BS group ( $p=0.03$ ), but not in neuro-BS group ( $p=0.081$ ). Concerning the amplitude, values obtained in parietal region in both BS ( $p=0.008$ ) and neuro-BS groups ( $p=0.033$ ) and obtained from frontal region for BS group ( $p=0.044$ ) were significantly lower than control group. According to PASAT results, controls performed better when compared both to BS and neuro-BS groups.

• **Conclusion:** BS group displayed similar electrophysiological changes and PASAT results compared to controls. Therefore our results suggested that P300 and PASAT might be used as objective methods in detecting subtle involvement that may be due to impairment of large scale attention-executive function-working memory network in patients with BS without overt neurological involvement.

• **Key Words:** Behçet's disease, PASAT, event-related potentials, clinical neurophysiology. *Nobel Med 2009; 5(2): 29-34*

## ÖZET

### SUBKLİNİK NÖRAL TUTULUMLU BEHÇET SENDROMUNDA OLAYA İLİŞKİN POTANSİYELLERİN VE PASAT'IN DEĞERLENDİRİLMESİ

• **Amaç:** Behçet Sendromu (BS) santral sinir sistemini etkileyebilen inflamatuvar bir hastalıktır. BS'li hastalarda özellikle kognitif fonksiyonların etkilendiği subklinik tutulum gözlenebilmektedir. Bu çalışmanın amacı BS'li olgularda subklinik tutulumun varlığını araştırmaktır.

• **Materyal ve Metod:** Bu çalışmada olaya ilişkin potansiyeller (P300) ve Paced Auditory Serial Addition Test (PASAT) kullanılmıştır. Bu çalışmaya nöroradyolojik görüntülemeleri normal olan BS olguları (14 olgu, 8 erkek 6 kadın; ortalama yaş 35,9±8,2), Nöro-Behçet (NBS) olguları (14 olgu; 9 erkek 5 kadın; ortalama yaş 36,7±8,3) ve sağlıklı bireyler (12 olgu; 8 erkek 4 kadın; ortalama yaş 32,2±5,3) dahil edilmiştir.

• **Bulgular:** Santral ve frontal bölgeden elde edilen

P300 latanslar BS ( $p=0,006$ ,  $p=0,039$ ) ve NBS ( $p=0,019$ ,  $p=0,026$ ) grubunda kontrol grubuna göre anlamlı uzun bulundu. Pariyetal bölgeden elde edilen latans BS grubunda anlamlı uzun ( $p=0,03$ ) iken NBS grubunda anlamlılık saptanmadı ( $p=0,081$ ). Pariyetal bölgeden elde edilen amplitüd değerleri BS ( $p=0,008$ ) ve NBS ( $p=0,033$ ) grubunda, frontal bölgeden elde edilen amplitüd değerleri ise BS grubunda ( $p=0,044$ ) kontrol grubuna göre anlamlı düşük saptandı. PASAT sonuçlarına göre kontrol olgularında BS ve NBS olgularına göre daha iyi yanıtlar elde edilmiştir.

• **Sonuç:** BS olguları kontrol grubu ile benzer PASAT değerleri ve elektrofizyolojik değişiklikler göstermiştir. Sonuçlarımıza göre P 300 ve PASAT belirgin nörolojik bulgusu olmayan BS olgularında geniş ölçekli dikkat yürütücü işlevler ve çalışma belleği ağının etkilenmesine bağlı erken nörolojik tutulumun saptanmasında objektif bir metod olarak kullanılabilir.

• **Anahtar Kelimeler:** Behçet hastalığı, PASAT, olaya ilişkin potansiyeller, klinik nörofizyoloji. *Nobel Med* 2009; 5(2): 29-34

## INTRODUCTION

Behçet's Syndrome (BS) is a multi-system inflammatory disorder characterized by uveitis and recurrent orogenital ulcers. It is thought to be due to an autoimmune vasculitis involving small blood vessels. Although any part of the neuraxis can be involved, central nervous system (CNS) involvement is well recognized and occurs in about 5% of the cases in the months and years following systemic manifestations.<sup>1-4</sup> A subclinical involvement, particularly affecting cognitive functions, might be observed in patients with BS without neurological manifestations.<sup>5</sup>

Subclinical neural involvement might be evaluated by using long-latency evoked potentials and Paced Auditory Serial Addition Test (PASAT). Although none of them is useful for localizing neurological lesions, both are able to detect involvement of the neural substrates required to obtain normal results.

The long-latency evoked potentials are also known as cognitive evoked potentials or endogenous event-related potentials (ERPs). P300 is the best known of the ERPs. Although the literature is scant, in some studies addressing P300, prolonged latencies were elicited. This finding interpreted as a reflection of subclinical neurological involvement in BS patients without neurological manifestations.<sup>6, 7</sup>

Following structures need to be intact for eliciting normal P300 responses: prefrontal cortices, posterior parietal regions, medial temporal structures including hippocampi, other primer cortical and association cortices, and neural networks responsible for memory, spatial and general attention.<sup>8</sup>

The information processing time can be evaluated in terms of various time-limited performances. PASAT is widely used for this purpose. PASAT investigates knowledge, memory, auditory reception and processing speed, speech generation, focusing and sustaining attention and basic mathematical ability (calculation). Positron emission tomography (PET) studies showed prevalent discontinuous foci in subtemporal gyrus, bilateral frontal and parietal regions, cingulate gyrus frontal region and bilateral cerebral regions that were activated during PASAT.<sup>9, 10</sup>

BS with neurological manifestations is mainly a disease of motor compartment of the CNS, but it is frequently accompanied by cognitive dysfunction.<sup>11, 12</sup> Cognitive dysfunction of neuro-BS is characterized by memory problems, particularly retrieval type, and dysexecutive syndrome. Attention deficits were also reported before. These cognitive problems are not necessarily consistent with the extent of neurological involvement. They sometimes become apparent and show progression while the disease is relatively stable.<sup>1, 5, 12</sup> →

The aim of this study was to find out any evidence of subclinical involvement in patients with BS. We compared BS patients with controls by using cognitive ERPs and PASAT to detect the involvement patterns in BS patients if exists. We also compared BS patients with neurological involvement (neuro-BS patients) with controls.

## MATERIAL and METHOD

### Study population

This was a prospective, controlled study. The study population comprised 3 groups: BS patients without neurological involvement (BS group), patient with neuro-BS (neuro-BS group) and healthy subjects (control group). All patients fulfilled the criteria of the International Study Group for BS. BS group was being followed at the outpatient clinic for Behçet's disease in the Rheumatology Department of Istanbul University Cerrahpaşa School of Medicine. They never had neurological symptoms or signs. The neurological examinations and cranial MRI's of the patients were normal.

Neuro-BS group was being followed in both Neurology and Rheumatology Departments of Istanbul University Cerrahpaşa School of Medicine. They had neurological manifestations and parenchymal involvement determined by magnetic resonance (MR) imaging.

Control group consisted of healthy subjects with no history of neurological, systemic, or psychiatric diseases. They had similar age distribution and levels of education to the patients as shown in Table 1.

Exclusion criteria for all the patients and control subjects included psychiatric disorder, other systemic disease (e.g., diabetes, chronic renal failure) and the use of any drug during 1 week. Informed consents were obtained from all patients and controls prior to their inclusion to the study. This study had also been approved by local ethical committee.

	Control	BS	Neuro-BS	p value
No of subjects	12	14	14	NS
Age	32.2±5.3	35.90±8.2	36.7±8.3	NS (*)
Sex (M/F)	8/4	8/6	9/5	NS (**)
Education level	6.3±1.5	7.2±2.1	7.2±2.3	NS (*)
Age of onset (BS)	-	28.8±5.3	29.7±8.6	NS (***)
Age of onset (Neurological involvement)	-	-	34±9.17	-

BS: Behçet Syndrome, \*: One way ANOVA, \*\*:  $\chi^2$  test, \*\*\*: Student's t-test

### The evaluation of ERPs using the P300 test

The P300 tests were performed in the EMG laboratory by using a Nihon Kohden Neuropack MEB-5504K EMG-EP device. The proposals of the International Clinical Neurophysiology Federation were taken into consideration for the adjustments made in the application of the P300 tests.<sup>13</sup> Each patient seated on a comfortable chair in a quiet room with their eyes lightly closed. Prior to the recordings, experimental procedures were explained to the subjects and a brief application was carried out to identify the main stimulus. ERPs were recorded on both hemispheres from the frontal (F3-F4), central (C3-C4) and parietal (P3-P4) electrode sides of the 10-20 system (Figure 2a,b,c). The reference electrode was positioned on the right mastoid, and the ground electrode was placed on the left frontal area. The electroencephalographic activity of more than 50µv was rejected.

A high frequency filter was set at 70 Hz and a low frequency filter at 0.1 Hz. The impedance was designated as 5 kilo-ohms and sensitivity adjustment was 50 microvolt. Recording times were 100 msec pre- and 1000 msec post-stimulus. With the help of a headphone, a sound of 65dB was applied arbitrarily throughout the testing period as 80% frequent stimulus and 20% infrequent stimulus. The infrequent stimulus had a frequency of 2000 Hz, and that of the frequent stimulus was 1000 Hz. Amplification (rise-time) and de-amplification (fall-time) times of 10 msec were designated for both types of stimuli. The subjects were asked to listen to the stimuli at a rate of 0.5 Hz. An average curve was obtained from the 50 curves. The same test was applied to each subject twice. The average of the two curves was used when the P300 latency and amplitude values were being measured, and the new value was used for statistical analysis. The value between N200 and P300 peak was taken as the amplitude (Figure 1).

### The PASAT and other neurocognitive tests

All subjects were informed about the procedure for the PASAT. They have listened to a sequence of numbers recorded on a tape with 3 seconds intervals. When they heard the first two numbers, they pronounced the sum of these two numbers out loud. After the third number, they calculate the sum of the second and the third numbers. The patients were initially given a practice test requiring 10-30 such calculations. Patients and control subjects who successfully completed this test were then given another test requiring 60 calculations with numbers given in 3 sec-intervals. The number of correct calculations was taken as the PASAT score. The →

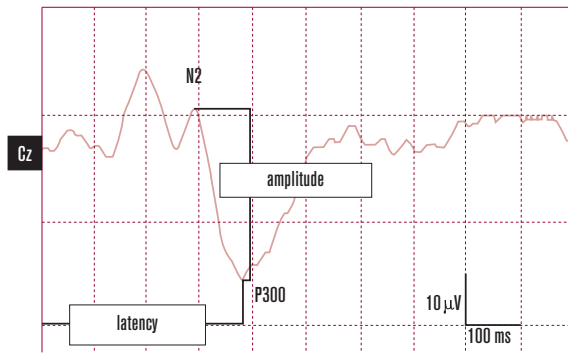


Figure 1. P300 amplitudes and latency

scores were converted to percentage and used in the statistical analysis. Minimalist test and Hamilton depression scale were performed in all subjects in order to exclude depression and dementia.<sup>14, 15</sup>

### Statistical analysis

In general standard deviations were not in broad ranges thus instead of nonparametric tests, the test results obtained from all study groups were evaluated using parametric one-way analysis of variance (ANOVA). The significant data by the ANOVA were analyzed by Dunnett's test. The gender comparison between each group was evaluated using Chi square test while other demographic data was analysed by ANOVA. Significance was assumed at  $p < 0.05$ .

## RESULTS

BS group consisted of 14 patients (8 men and 6 women, mean age  $35.9 \pm 8.2$  [20-50] years) while the Neuro-BS group consisted of 14 patients (9 men and 5 women, mean age  $36.7 \pm 8.3$  [26-50] years). The control group consisted of 12 healthy subjects (8 men and 4 women, mean age  $32.2 \pm 5.3$  [25-42] years). The demographic and disease clinical data are given in Table 1 where it is seen that, age, gender, educational and disease related data are similar for all groups. In neuro-BS group 1 patient had venous sinus thrombosis, 6 patients had pontin lesions, 5 patients had mesencephalic and diencephalic lesions, 1 patient had supratentorial and pontin lesions and 1 patient had cervical lesions.

The P300 latencies elicited from central and frontal electrodes were significantly longer for the BS ( $p=0.006$ ,  $p=0.039$ ) and neuro-BS ( $p=0.019$ ,  $p=0.026$ ) groups compared to controls. In the parietal derivation latency was significantly longer in the BS group ( $p=0.03$ ), but not in the neuro-BS group ( $p=0.081$ ) compared to control. There was no amplitude difference in the central derivation when BS and neuro-BS groups compared to controls. However, the amplitude values

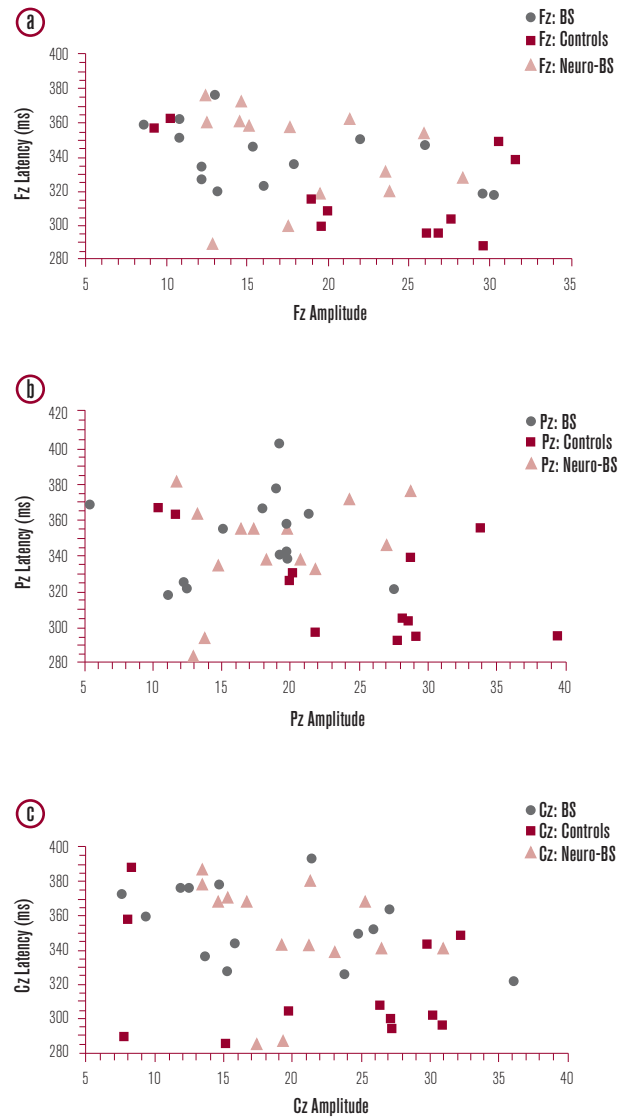


Figure 2 a,b,c. ERPs recorded from a) frontal (F3-F4), b) parietal (P3-P4) and c) central (C3-C4) electrode sides of the 10-20 system

obtained in parietal derivation were significantly lower in both the BS ( $p=0.008$ ) and neuro-BS groups ( $p=0.033$ ) than values obtained from the control group. In addition, the amplitude values obtained from the frontal derivation for the BS group ( $p=0.044$ ) were significantly lower than control group. The electrophysiological P300 and PASAT results in study groups are given in Table 2.

The ages at onset of the disease and P300 results were similar in the BS and neuro-BS group. There was no significant relationship between the duration of neurological involvement, P300 amplitude, and latency values in neuro-BS patients. According to the PASAT results the control group was on average 75.2% successful, whereas, the BS patients scored an average of 52.9% and the neuro-BS patients 53.4%. A significant difference was observed both in the BS ( $p=0.048$ ) and neuro-BS group ( $p=0.05$ ) as compared →

to the controls. In fact cognitive evoked potentials are very sensitive to changes in alertness and vigilance, thus the patients with poorest results might be clinically tired.

## DISCUSSION

In this study, we compared demographically similar BS and neuro-BS groups with healthy controls, and observed that both BS and neuro-BS groups were significantly different from control group in terms of P300 latencies, amplitudes, and PASAT performance. Nervous system involvement is one of the most serious manifestations of BS affecting the quality of life. In some cases without neurological signs and symptoms, there is a possibility of sub-clinical involvement.<sup>1, 3</sup> Sub-clinical involvement of the central nervous system may be due to widespread microscopic findings rather than the macroscopic lesions.<sup>16</sup>

Electrophysiological studies such as stimulus related evoked potential and event-related potential might provide functional information about neural involvement in BS. High incidences of evoked potential abnormalities have been reported in patients with neurological symptoms.<sup>17-20</sup> Besides electrophysiological studies, functional imaging studies of the brain using SPECT also revealed abnormal results in BS patients without neurological involvement.<sup>21-24</sup> Studies about the changes in mental status in BS patients with neurological manifestations were usually based on clinical symptomatology.<sup>12</sup>

There are a few studies P 300 studies on sub-clinical involvement in BS patients without neurological manifestations. Keçeci et al.<sup>6</sup> reported that P300 latencies were longer in BS patients without neurological impairment and their patients had also longer motor response time values. They have attributed these results to sub-clinical involvement of neuronal circuitry and thought that it might be due to small vessel vasculitis. Recently another study on a group of BS patients without neurological involvement revealed that the habituation of auditory event-related potentials, which may be accepted as the simplest form of implicit learning, was impaired. Prolongation of the P300 latencies in the patients compared to the controls was also a consistent finding in this study.<sup>16</sup> In a recent study, Gökçay et al.<sup>25</sup> showed that P300 latencies elicited from patients with neuro-BS were longer than that of healthy controls and BS patients without neurological involvement. They have also reported neuropsychological test abnormalities especially in

**Table 2:** The electrophysiological P300 and PASAT results in study groups

	Groups			p value		
	Control (n=12)	BS (n=14)	Neuro-BS (n=14)	Group differentiation	Control vs. BS (*)	Control vs. Neuro-BS (*)
Frontal latency	316.54±27.71	340.42±18.35	342.14±27.51	F=4.33 p<0.05	0.039	0.026
Central latency	312.72±28.30	344.71±19.33	340.00±27.34	F=6.10 p<0.02	0.006	0.019
Parietal latency	322.18±28.41	349.71±24.84	344.85±28.41	F=3.79 p<0.05	0.030	NS
Frontal amplitude	23.43±7.70	17.06±7.18	18.60±5.25	F=3.15 NS	-	-
Central amplitude	21.6±9.39	18.33±7.86	19.50±5.08	F=0.63 NS	-	-
Parietal amplitude	25.05±8.55	17.15±5.47	18.60±5.37	F=5.42 p<0.05	0.008	0.033
PASAT (%)	75.2±22.03	52.90±20.97	53.40±21.92	F=3.42 p<0.05	0.04	0.05

NS: Not Significant, \*: Dunnet's test, BS: Behçet Syndrome

attention (40%) and memory (30%) in patients with neuro-BS. This was not the case for BS patients without neurological impairment and controls. The degree of neuropsychological abnormalities is correlated with the extent of the prolongation of P300 latencies especially for the attention.<sup>25</sup> Özişik et al.<sup>26</sup> were unable to show any P300 latency difference and neuropsychological abnormality in BS patients without neurological involvement. The origin of P300 wave may be related to the neuronal activity of multiple brain regions including the diencephalon, parietal lobe association cortex, frontal lobe, hippocampus and medial temporal structures.<sup>25, 26</sup> P300 has been widely used to study age-related cognitive dysfunction, because it reflects attention and memory process. P300 latency is directly associated with cognitive capability in both normal and patient population.<sup>26</sup>

As we noted above, a large neuronal circuitry working in harmony is required for obtaining normal PASAT scores as well as for eliciting normal P300 responses. The main network that could be involved in both tests might be working memory-executive functions-attention circuit. The transmodal epicenters for this network were called as heteromodal (dorsolateral) prefrontal cortex and posterior parietal cortex by Mesulam.<sup>8</sup> These epicenters are directly connected to each other, but they are also connected via striatum and thalamic nuclei that were mostly involved structures in patients with neuro-BS in various clinical and imaging studies.<sup>11, 27</sup> The pattern of cognitive impairment reported by the studies cited above is also consistent with the involvement of suggested network. Extensive neuropsychological battery application might be time consuming and expensive for both physicians and patients. Although PASAT could not emphasize an extensive neuropsychological result, prolongation of P300 latencies associated with →

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abnormal PASAT scores, assessing the working memory, attention and calculation ability, might give some clues for subclinical neural involvement in BS. PASAT has been developed to assess the effects of traumatic brain injury on cognitive functioning. It has also been extensively used for investigating cognitive abilities in multiple sclerosis patients as well as in patients with whiplash injury, lupus, hypoglycemia, renal transplantation, and depression.<sup>2, 11</sup>

We have used PASAT as a supportive measure to our P300 results and found that both patient groups performed similarly and the results were worse when compared to the controls'. The similar pattern of test results obtained from both BS group and neuro-BS group might be interpreted as a result of widespread microscopic involvement of the brain rather than focal lesions that have been seen in neuroimaging. The main limitation of our study and previous studies

is that BS patients without neurological involvement who had prolonged P300 latencies, patients with abnormal neuropsychological test results but without obvious neurological findings, have not been followed for long periods for the development of neurological involvement.

In conclusion in our study both P300 and PASAT were found to be easily applicable and informative tests in assessing subclinical involvement in patients with BS without neurological manifestations. We suggest that both tests may be used as additional choices of investigation when someone intends to assess subclinical involvement in BS. Further extensive and prospective studies and longer follow-up periods are needed to support these findings and to find out if abnormal P300 values and PASAT scores provide any evidence about the conversion rates from BS to neuroBS.

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