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Cognitive Event-Related Potential and Neuropsychological Findings in Behçet's Disease without Neurological Manifestations

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OZISIK, H.I., KARLIDAG, R., HAZNECI, E., KIZKIN, S. and OZCAN, C. *Cognitive Event-Related Potential and Neuropsychological Findings in Behçet's Disease without Neurological Manifestations*. Tohoku J. Exp. Med., 2005, **206** (1), 15-22 —— Behçet's disease (BD) is a multisystem inflammatory disorder characterized by recurrent oral and genital ulcers and uveitis. BD patients without neurological involvement frequently have mild neurological symptoms. The aim of this study was to evaluate whether BD patients without neurological involvement have any changes in cognitive functions. Twenty BD patients without neurological involvement and 13 control subjects were included in the study and were analyzed by neurophysiological and neuropsychological examinations. The cognitive event-related potentials (P300) were recorded from the frontal, central and parietal areas of the right and left hemispheres of the patients and control subjects. Likewise, all individuals were evaluated with neuropsychological tests. In contrast to a study with similar design, we did not find any difference between the cognitive event-related potentials values of BD patients without neurological involvement and the control subjects. All BD patients without neurological involvement exhibit normal results of the neuropsychological test. In conclusion, the results of neuropsychological tests and cognitive event-related potentials values in BD patients without neurological involvement are indistinguishable from those in control subjects and no alteration of cognitive functions is present. ———— cognitive event-related potentials; neuropsychological tests; Behçet's disease

Behçet's disease (BD) is a multisystem inflammatory disorder characterized by recurrent oral and genital ulcers and uveitis. The disease has a higher prevalence in the Middle East, in the southern and eastern part of the Mediterranean area and in Japan (Stigsby et al. 1994). The prevalence has been estimated to be 5 in 100,000 population (Stigsby et al. 1994). The eyes, skin and mucosa, joints, vascular system (mainly veins), lungs, gastrointestinal tract and nervous system are affected (Akman-Demir et al. 1999). Neurological involvement, most frequently as para- and quadriparesis, cerebellar ataxia, pseudobulbar palsy, cranial nerve palsies and aseptic meningoencephalitis, has been reported in 5 - 49% of patients with BD (Stigsby et al. 1994, 2000; Kidd

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et al. 1999). Although any part of the neuraxis may be involved, the disease has a predilection for the diencephalon, brain-stem and spinal cord (Stigsby et al. 2000).

Electrophysiological studies such as stimulus-related evoked potential and event-related potential may provide functional information complementary to magnetic resonance imaging (MRI) about neural involvement in BD, and a high incidence of evoked potential abnormalities have been reported in patients with neurological symptoms (Besana et al. 1989; Rizzo et al. 1989; Nakamura et al. 1994; Stigsby et al. 1994). However, BD patients without neurological manifestations also frequently show abnormal Neurophysiological test results (Stigsby et al. 1994, 2000; Keçeci and Akyol 2001).

Stimulus-related evoked potentials represent an obligative neuronal response to a given stimulus and provide information about the afferent sensory functions of the neuroaxis (Aminoff and Eisen 1992). Cognitive event-related potentials (ERPs) occur only when the subject is selectively attentive to the stimulus, and ERPs have become popular as a tool for assessing cognitive dysfunction (Oken et al. 1987; Goodin et al. 1992). Many different components of the cognitive ERP have been identified including N100, P200, N200, P300 and N400. Most clinical studies have been concerned primarily with the more easily identified N100 and P200 components in response to the non-target tone and report that this is not associated with attention (Aminoff and Eisen 1992) However, a more recent study has shown that P100 is associated with early attentive processes (Ozaki et al. 2004). The P300 test is one of the well-known cognitive ERPs. The P300 components of cognitive ERP appear following infrequent and novel stimuli. The origin of the 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 lobe structures (Gökçay et al. 2004). P300 has been widely used to study age-related cognitive dysfunction, because it reflects attentive and memory processes. Abnormalities of cognitive ERP have been reported in diseases such as Parkinson's disease, Alzheimer's disease, other dementias, multiple lacunar infarcts, metabolic and toxic encephalopathies, Huntington's disease, multiple sclerosis, human immune deficiency virus infection and schizophrenia (Cohen et al. 1983; Rosenberg et al. 1983; Pfefferbaum et al. 1984; Gordon et al. 1986; Goodin et al. 1987, 1992; Kimura et al. 1990; Polich et al. 1992; Ito et al. 1994). P300 amplitude is an index of brain activity that is required in the maintenance of working memory. It is also proportional to the amount of attentive resources devoted to a given task and has been associated with superior memory performance. P300 latency is an index of the processing time. It is a sensitive temporal measure of the neural activity underlying the processes of attention allocation and immediate memory (Knight and Scabini 1998). This association is also supported by results indicating that P300 latency increases as cognitive capability decreases from dementing illness. Thus, P300 latency is directly associated with cognitive capability in both normal and patient populations (Knight and Scabini 1998).

We report the results of cognitive ERPs of the left and right hemisphere regions (frontal, central and parietal) in BD without neurological manifestations. The purpose of this study was to investigate whether cognitive ERPs and neuropsychological test alterations exist in BD patients without neurological manifestations.

Materials and Methods

Subjects

The patients diagnosed as having BD and included in the study were among those being followed-up at the dermatology department. All patients fulfilled the clinical diagnostic criteria of the International Study Group for Behçet's disease (International Study Group for Behçet's disease 1990). There were 9 women and 11 men whose ages ranged from 17 to 52 years with a mean age of 31 ± 9.2. All subjects were examined neurologically. All of them had no previous or recent neurological symptoms or signs. The duration of BD ranged from 1 to 30 years with a mean duration of 7.9 ± 8.7 years. Eight patients were not on any medication. Twelve patients were being treated with colchicine and/or immuno-

suppressive.

Healthy control subjects with no history of neurological or psychiatric disease were matched for age and sex with the patient group. This group consisted of 7 women and 6 men whose ages ranged from 20 to 40 with a mean age of 30.7 ± 6.3 years.

Exclusion criteria for all the patients and control subjects included neurological and psychiatric disorders, the presence of any lesion in computerized tomography or magnetic resonance imaging, other systemic disease (e.g., diabetes, chronic renal failure) and the use of any drugs at least once during the last week.

P300 recording procedure

The P300 was recorded using the MEM – 4,200 K evoked potential recorder (Nihon Kohden, Tokyo). An "oddball paradigm" of auditory stimuli was used to evoke the P300. The oddball paradigm consists of the presentation of a sequence of two different frequency tones, one of which occurs frequently (the non-target stimulus) and the other infrequently (the target stimulus). The sequence of the target and non-target stimuli was pseudo-random, with the constraint that no two target tones, which amounted to 20% of the stimuli presented, occurred consecutively. A 2,000 Hz tone was used for the target stimulus and a 1,000 Hz tone served as the non-target stimulus. Informed consent was obtained from all patients and control subjects prior to their inclusion in the study. All subjects were seated in a comfortable chair in a quiet room with their eyes loosely lightly closed, the experimental procedures were explained to the subjects, and recordings were then made. Patients and control subjects were instructed to keep a running mental count of the target tones. Their attention was verified by comparing the actual target tone number with the number counted by the participant. The tests were performed twice each time and the trace was rejected and the test repeated in cases of at least a 15% discrepancy between the numbers of delivered and counted target stimuli.

Silver/silver chloride disc electrodes (adult size, disc diameter 9 mm, Touchproof Part No. 19329T, TECA Accessories by Medelec) anchored with adhesive electrolyte gel were used to record the P300. Cognitive ERPs were recorded on both hemispheres from the frontal (F3 - F4), central (C3 - C4) and parietal (P3 - P4) electrode sites of the 10 - 20 system. The reference electrodes recorded from both auricula.

An electroencephalographic activity of more than 50 μv was automatically rejected. The input impedance was kept at less than 3 kilo-ohms. A high-frequency filter was set at 70 Hz and a low-frequency filter at 0.1 Hz. Alternating tone bursts, with a starting condensation phase of 10 milliseconds rise/fall time, 100 milliseconds duration, and intensity 70 dB greater than the normal hearing threshold at the rate of one every 2 seconds were used.

Electroencephalography epochs of 100 milliseconds before and 900 milliseconds after the onset of each tone were amplified and stored digitally by a computer system. The task was repeated to confirm reproducibility. The cognitive ERPs recording was repeated twice in each case and at the least 30 electroencephalography epochs following the target tones were averaged.

The peak latencies of the ERP waves (N100, N200, P200 and P300) were measured at the electrode sites. The N100 and P300 waves were used for statistical evaluation. Their amplitudes at all sites were then measured between the baseline to peak for each component. The peak amplitude and latency of the N100 components were measured from averages elicited by non-target (frequent) and target (infrequent) tones. N100 was scored at the largest negative value between 80 and 150 milliseconds after the stimulus onset. P300 peaks were measured as the largest positive value between 250 and 600 milliseconds from averaged cognitive ERPs to target (infrequent) tones.

For statistical analysis the N100 and P300 latency and amplitude measurements were compared using the Mann-Whitney's U-test.

Neuropsychological testing was performed in all subjects. Each subject was evaluated by the Wechsler Memory Scale-Revised (WMS-R). The performance of the patients was scored particularly in regard to attention and memory function. The Mann-Whitney's U-test and Spearman's correlation test were used for the mean comparisons. Significance was assumed at $p < 0.05$.

Results

Twenty patients met the entry criteria and were accepted for the study. The ERPs were recorded in all the subjects of the patient and control groups (Figs. 1 and 2). The latency and amplitude values of the N100 wave following target and non-target stimuli did not show a statistically significant difference between the patient and control groups for the frontal, central and parietal regions of the right and left hemispheres (Tables 1

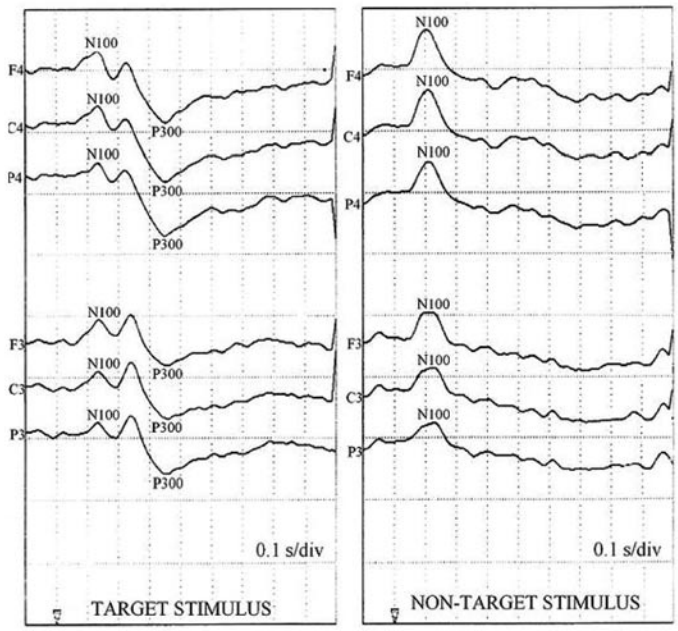

Fig. 1. Trace sample of P300 recorded from frontal, central and parietal regions in the right and left hemispheres of a Behçet Disease patient.

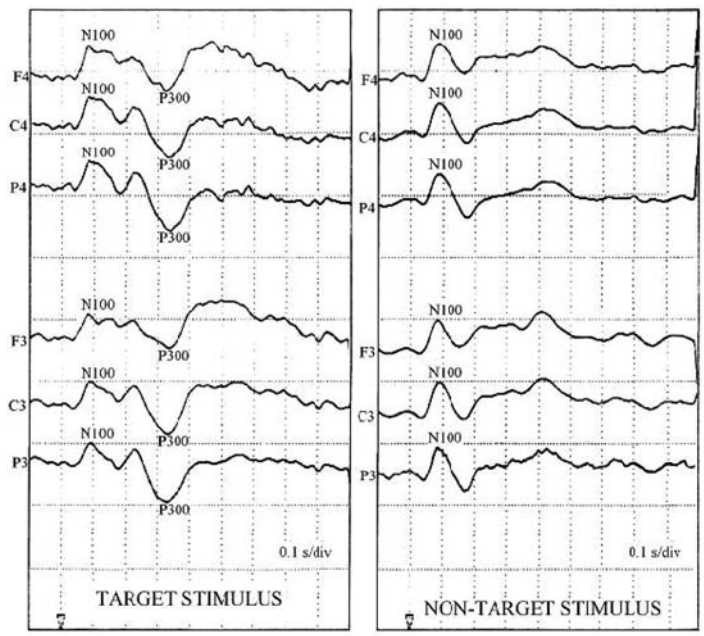

Fig. 2. Trace sample of P300 recorded from frontal, central and parietal regions in the right and left hemispheres of a control subject.

and 2). The mean P300 latency and amplitude values of BD patients without neurological manifestations and those of the control subjects are shown in Table 3. Similarly, P300 latency and amplitude values recorded in BD patients without neurological manifestations were not significantly different from the values of normal controls.

All BD patients without neurological mani-

TABLE 1. *The comparison of N100 latencies and amplitudes obtained with target stimulus from patients and controls*

Target Stimulus						
		Right*		Left*		p**
		Patients	Controls	Patients	Controls	
Frontal N100	Latency	91.44 ± 12.57	97.69 ± 21.02	99.44 ±15.63	100.15 ± 24.21	NS***
	Amplitude	8.44 ± 2.98	9.36 ± 3.60	8.60 ± 1.95	8.46 ± 3.62	NS
Central N100	Latency	91.58 ± 13.02	98.92 ± 18.05	99.26 ± 12.39	102.15 ± 21.31	NS
	Amplitude	9.55 ± 3.18	8.80 ± 3.70	9.72 ± 2.74	8.80 ± 4.50	NS
Parietal N100	Latency	93.68 ± 13.75	100.46 ± 18.53	97.26 ± 12.11	98.92 ± 21.87	NS
	Amplitude	7.76 ± 2.46	7.67 ± 3.77	8.23 ± 3.08	7.43 ± 3.57	NS

* Mean ± S.D. of latencies and amplitudes in frontal, central and parietal regions in the right and left hemispheres in patients with BD and controls.

** p value between right and left hemisphere sides of patients and controls.

*** NS, not significant.

TABLE 2. *The comparison of N100 latencies and amplitudes obtained with non-target stimulus from patients and controls*

Non-Target Stimulus						
		Right*		Left*		p**
		Patients	Controls	Patients	Controls	
Frontal N100	Latency	93.16 ± 12.86	100.80 ± 13.27	97.47 ± 14.87	101.20 ± 12.44	NS***
	Amplitude	8.93 ± 3.48	9.38 ± 3.39	8.47 ± 3.44	8.96 ± 3.72	NS
Central N100	Latency	93.16 ± 11.74	101.00 ± 16.03	98.00 ± 14.51	101.60 ± 12.32	NS
	Amplitude	9.19 ± 2.95	9.01 ± 4.11	10.19 ± 3.47	8.53 ± 4.24	NS
Parietal N100	Latency	94.11 ± 11.06	101.40 ± 16.92	97.37 ± 13.94	101.60 ± 12.32	NS
	Amplitude	8.02 ± 2.56	7.80 ± 4.34	8.98 ± 2.86	7.39 ± 3.81	NS

* Mean ± S.D. of latencies and amplitudes in frontal, central and parietal regions in the right and left hemispheres in patients with BD and controls.

** p value between right and left hemisphere sides of patients and controls.

*** NS, not significant.

festations had normal neuropsychological tests.

DISCUSSION

Behçet's Disease is a symptom complex. Neurological involvement has been reported in about 5 - 49% of patients with BD (Stigsby et al. 1994, 2000) but subclinical involvement without neurological signs and symptoms is possible. Frank onset of neurological involvement is commonly 4 - 6 years after the onset of BD. However, neurological involvement due to BD occurs prior to its characteristic oral and cutaneous lesions in some patients (Serdaroğlu 1998). Additionally, subclinical neurological involvement has been clearly demonstrated in some previous series and some of these patients have developed acute attacks during the clinical follow-up period (Serdaroğlu 1998). Early detection of neural in-

TABLE 3. *The comparison of P300 latencies and amplitudes obtained from patients and controls*

		Right*		Left*		p**
		Patients	Controls	Patients	Controls	
Frontal P300	Latency	336.7 ± 18.8	348.3 ± 21.3	337.9 ± 17.1	343.1 ± 21.0	NS***
	Amplitude	12.7 ± 6.8	16.6 ± 10.8	12.6 ± 5.6	14.1 ± 6.8	NS
Central P300	Latency	340.9 ± 22.7	348.9 ± 22.2	338.8 ± 16.8	343.8 ± 21.4	NS
	Amplitude	17.6 ± 8.6	19.3 ± 12.2	17.9 ± 6.9	16.9 ± 7.6	NS
Parietal P300	Latency	344.2 ± 24.7	352.3 ± 22.1	339.9 ± 18.2	346.2 ± 21.4	NS
	Amplitude	19.0 ± 8.6	20.2 ± 11.6	19.0 ± 6.7	17.3 ± 8.1	NS

* Mean ± S.D. of latencies and amplitudes in frontal, central and parietal regions in the right and left hemispheres in patients with BD and controls.

** p value between right and left hemisphere sides of patients and controls.

*** NS, not significant.

volvement may provide early establishment of appropriate treatment for neuro-Behçet's disease.

Visual (VEP), brainstem (BAEP), somatosensory (SEP) and cognitive evoked potentials are expected to be normal in BD patients but there are studies reporting abnormal BAEP, VEP and MEP values in 31%, 25% and 28% of patients with BD without neurological manifestations respectively suggesting subclinical involvement (Stigsby et al. 1994, 2000; Nakamura et al. 1994; Parisi et al. 1996).

BD with neurological manifestations is mainly a disease of the motor compartment of the CNS, frequently accompanied by cognitive dysfunction (Ahmed et al. 1993; Serdaroğlu 1998; Akman-Demir et al. 1999; Kidd et al. 1999; Siva et al. 2001). The reports are so far inconclusive on whether there is cognitive impairment in BD patients without neurological involvement. Neuropsychological and Neurophysiological tests are used to evaluate cognitive functions. We studied the subclinical impairment of cognitive functions in BD patients who had normal neurological findings with neuropsychological and Neurophysiological studies. Although the brain stem is frequently involved in Behçet's disease, designing neuropsychological and Neurophysiological tests which evaluate cerebral functions to cover as wide an area as possible is important to detect minor changes as the neuraxis may be involved at any site. There are two studies on P300 being utilized to detect subclinical cognitive impairment in BD patients without neurological manifestations (Keçeci et al. 2001; Gökçay et al. 2004). Although one of these studies has recorded from only one cerebral region and the other study from two cerebral regions, we recorded potentials from six separate regions in both cerebral hemispheres and investigated whether these patients may have moderate regional differences. In contrast to the other two studies, we also studied the characteristics of the N100 wave in response to target and non-target stimuli as it has been shown to be important for early attentive processes (Ozaki et al. 2004). We did not find a difference in the BD group as compared to the control subjects. Keçeci et al. (2001) showed prolonged P300 latencies at Cz electrode while Gökçay et al. (2004) showed that the patient group without neurological manifestations had normal P300 latency and amplitude at Fz and Cz electrodes as in our findings. However, sex distribution of the patient group of Gökçay et al. (2004) was different from the patients of Keçeci et al. (2001) and our patient group and sex were significant parameters influencing P300 latency (Hoffman et al. 1999; Reese et al. 2003). When we analyze the three studies and compared the records from a single cranial region, the P300 latencies and amplitudes recorded from the central

cranial region of Behçet's patients without neurological involvement are similar. However the latency values of the control group of Keçeci et al. (2001) are much lower than the latency values of the control groups of the other two studies. The low latency values of the control group of Keçeci et al. (2001) may explain the difference in latency that they reported between their patient group and the control subjects.

As may be seen from the different results of the three studies, the use of cognitive ERPs in evaluating and monitoring CNS disease activity in BD is problematic as distant pathological processes such as edema, inflammation, vasculitis, demyelination, and atrophy may account for the pathophysiology seen during different stages of neurological involvement. It may therefore be useful to record P300 waves from many different cerebral regions in BD.

Changes in mental status in BD with neurological manifestations have been observed and reported for many years (Kawakita et al. 1967), but these studies were based on clinical symptomatology. In one study memory and attention deficits were demonstrated as the predominant cognitive impairments in BD patients with neurological manifestations in neuropsychological tests (Öktem-Tanör et al. 1999). However, some authors have reported that neuropsychological tests could be useful in detecting subclinical involvement in asymptomatic patients as well (Ahmed et al. 1993). Our results showed that the patient group without neurological manifestations had normal neuropsychological test results.

This study was carried out in BD patients without neurological involvement. The cognitive functions of these patients were indistinguishable from those of control subjects, judged by the neuropsychological and neurophysiological tests. This result is different from some results reported previously. Our findings indicate that subclinical nervous system involvement in BD patients without neurological involvement is undetectable by neuropsychological and neurophysiological tests and this study has also verified the adequacy of neurobehçet diagnostic criteria in determining the cases with neurological involvement.

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