Is headache in Behçet's disease related to silent neurologic involvement?

E. Koseoglu[1], A. Yildirim[2], M. Borlu[3]

[1]Neurology Department, and [3]Dermatology Department, Faculty of Medicine, Erciyes University, Kayseri, Turkey;
[2]Neurology, Department, Nevşehir State Hospital, Nevşehir, Turkey;

Emel Koseoglu, Professor
Aslihan Yildirim, Neurology Specialist
Murat Borlu, Associate Professor

Please address correspondence and reprint requests to:
Prof Emel Koseoglu,
Neurology Department,
Faculty of Medicine,
Erciyes University,
Kayseri, Turkey.
E-mail: emelk@erciyes.edu.tr

Received on July 24, 2010; accepted in revised form on December 22, 2010.

Clin Exp Rheumatol 2011

Key words: headache, Behçet's disease

ABSTRACT

Objectives. *Headache is an interesting issue in Behçet's disease (BD). This study aimed to investigate if headache or a special type of headache was correlated with silent neurologic involvement in BD patients without any neurologic sign.*

Methods. *The study was performed on 120 BD patients (30 without headache, 30 with non-structural headache of BD and 30 with migraine headache, 30 with tension type headache) and 30 healthy control subjects. Some neurophysiologic tests of brain stem; temporalis muscle exteroceptive suppression periods (ESP) and brain stem auditory evoked potentials (BAEP) were performed in the patients, when they were not in an attack period of the disease, and control subjects to investigate the presence of silent neurologic involvement and the relation between headache and silent neurologic involvement.*

Results. *Some electrophysiological abnormalities, as right BAEP 1-5 interpeak latency prolongation ($p=0.01$) and and left ESP2 duration shortening ($p<0.005$), were seen in BD patients compared to healthy control subjects. Furthermore, the patients with non-structural headache of BD were found to have shorter ESP1 and 2 durations ($p<0.001$) and longer ESP1 latencies ($p<0.05$), with respect to the other patient subgroups with different types of headache and healthy control group, showing brain stem pathology. Additionally, they had longer right BAEP 3-5 interpeak latency as compared to the patient subgroup without headache ($p=0.001$).*

Conclusions. *There is a silent neurologic involvement in BD and this involvement may be in relation with a particular type of vascular headache, named as non-structural headache of BD. So, in clinical evaluation of BD patients, this type of headache may be considered as a warning message for neurological involvement.*

Competing interests: none declared.

Introduction

Behçet disease (BD) is a multisystem vascular-inflammatory disease of unknown origin. Neurological involvement was reported to occur in 5.3–14.3% of patients in three prospective studies from Turkey (1), Iran (2), and Iraq (3), which looked specially at the frequency in multidisciplinary centres with special interest in BD. In an autopsy series, 20% of 170 cases of patients with BD showed pathological evidence for neurological involvement (4).

Central nervous system (CNS) involvement in BD can be categorised as parenchymal and non-parenchymal CNS involvement (5). Some authors have reported that silent neurologic involvement may also occur in BD (6-9). They showed that some BD patients had abnormalities on neurologic examination and/or abnormal findings on neurophysiologic tests on neurologic evaluation performed routinely or due to the complaint of headache.

The relationships between different clinical manifestations of the disease were studied by some groups of investigators. They thought that identification of associations of the manifestations could help doctors not only better understand the pathogenesis of the disease, but also guide therapeutic decisions. Some found significant positive or negative relationships (10-12), but Arida *et al*. in a recent study with a detailed statistical evaluation (13) did not find any relationship. Nevertheless, these investigators did not consider headache in their evaluations.

Headache is an interesting issue in BD. It is seen more frequently in BD patients than in the normal population (14). In a prospective study on BD patients without neurologic attack (9), some patients with headache and/or minor neurologic clinical or electrophysiologic findings developed neurologic attacks in a seven-year follow-up period. These studies pointed that headache and/or

neurophysiological test abnormalities in BD patients showed a silent neurological involvement which could evolve into neurological attacks of BD. Furthermore, some authors developed a form which proved to be a reliable instrument for assessing general BD activity, in which headache was placed among the clinical features showing the disease activity (15). Additionally, in some studies, a bilateral frontal, paroxysmal throbbing headache was defined in BD patients (1,16). Saip *et al*. (16) called this type of headache 'non-structural headache of BD and found it commonly associated with exacerbations of mucocutaneous symptoms of the disease.

In this study, we aimed to investigate silent neurologic involvement with some neurophysiologic tests of the brain stem; temporal exteroceptive suppression period (ESP) and brain stem auditory evoked potential (BAEP); and to explore any correlation between silent neurologic involvement and headache, especially a headache type called non-structural headache of BD.

Patients and methods

The study was approved by the local Ethics Committee of Erciyes University and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Patient and healthy control group enrolment

One hundred and twenty BD patients and 30 healthy control subjects were enrolled in the study. The patients were selected from 250 patients without any known neurologic involvement with at least one year of disease duration, who were followed up at the Dermatology and Neurology Outpatient Clinics of Erciyes University. In this patient group, 60 and 90 of the patients had migraine type and tension type headache respectively. Thirty patients had a headache evaluated as non-structural headache of BD and all of them were enrolled in the study. For a reliable statistical analysis, thirty patients from each patient subgroup with no complaint of headache and with migraine type and tension type headache were selected randomly from the patient pool. The mean ages of the patient group and healthy control group were 34.26 (SD=10.39) and 30.50 (SD=8.18), respectively. The patient group comprised 72 female (60% of the patients) and 48 male patients (40%), while the healthy group consisted 17 females (56.7% of the healthy group) and 13 males (43.3%). There were no statistical difference between the distributions of age and gender in the groups (t=1.84, p>0.05 for age; χ^2=0.11, p>0.05 for gender). All subjects in the study were enrolled in the study after giving their written informed consent. The diagnosis of BD was made according to International BD Study Group criteria (17), while the diagnosis of neuro-BD was done mainly by clinical means.

Exclusion criteria of the patients:

- Presence of clinical neuro BD;
- Presence of BD attack with overt dermatologic signs;
- Cranial MRI showing brain stem lesion;
- MR venography showing dural sinus trombosis;
- Presence of headache associated with eye inflammation;
- Presence of depression;
- Presence of anxiety disorder;
- Presence of chronic pain;
- Presence of temporomandibular joint dysfunction;
- Use of drugs acting on seratonergic and/or noradrenergic system;
- Use of drugs which can affect ESPs such as Naloxane, acetyl saliyclic acid.

Clinical evaluation

The clinical evaluation of the all subjects was performed including history taking, physical and neurologic examinations. In history, complaint of headache was especially investigated. Laboratory screening (serum electrolytes, liver and renal function, sedimentation, basic haematologic parameters) of the subjects did not show any additional pathology. Also, in BD patients, detailed dermatologic examination were performed. All patients had normal results of cranial magnetic resonance imaging (MRI), MR venography and cerebrospinal fluid (CSF) examinations.

The headaches of the subjects were investigated. in a detailed way including timing, characteristics, localisation, triggering factors, accompanying symptoms. Headaches in the patients were classified according to the IHS criteria (18). The paroxysmal, throbbing, migraine like headache which was bilateral, predominantly frontal and mild-moderate severity, not fulfilling any type of headache in IHS classification was noted as non-structural headache of BD. In 18 of these patients, there were no accompanying symptoms of migraine. All of them had bilateral throbbing type headache which did not exacerbate with physical activity. Sixteen of these patients had mild severity headache, while 8 and 6 of them had moderate-to-severe and moderate severity headache, respectively. This type of headache, detected in 30 of our patients, did not fulfill the IHS criteria for migraine with or without aura, nor for tension-type headache, and therefore it was designated as the non-structural headache of BD. However, this type of headache may be classified as migrainous disorder (1.7) according to the 1988 IHS criteria (19) or as a probable migraine [1.6] according to the 2004 IHS criteria (18).

Electrophysiologic investigations

The electrophysiologic studies were performed with a two channel Medelec Synergy EMG and EP system instrument (Software version 10). All patients and healthy control subjects underwent the studies of BAEP and temporalis muscle ESP.

Brain stem auditory evoked potentials (BAEPs)

Bilateral BAEPs were recorded in a quiet and dim room. All subjects were requested to sit on a comfortable armchair and were instructed to avoid eye and head movements during the test. Monoaural click stimulations with durations of 0.1 ms were used. Stimulation level was determined by auditory threshold level plus 70 decibel (db) for each side. Stimulation frequency was 10 Hz. Ossiloscope sweep time was 10

ms. Amplifier filters was set between 100 Hz-2 kHz.

Recordings were performed using silver plated surface electrodes. Active electrodes were located on the both mastoid bone (A1 and A2). These electrodes were referenced to Cz electrode located according to 10–20 system. At least, 1000 responses were averaged for each analysis. Two traces of analysis, at least, were recorded and superimposed bilaterally.

The interpeak latencies of I-III, I-V and III-V were analysed.

Exteroceptive suppression periods of temporalis muscle (ESPs)

During the electrophysiologic investigation, subjects were instructed to make a forceful tooth clenching. The stimuli were delivered during this voluntary contraction to mental nerve at the border of the corner of mouth. Active recording electrodes were placed over the bellies of the temporalis muscles. Reference electrodes were put on the arcuses of the zygomatic bones. AgCl surface electrodes were used for the recording. Ossiloscope sweep time was 200 ms. Amplifier filter was set between 10 Hz-10 kHz. Gain was 0.2-0.5 mv/division. Stimulus duration was 0.1 ms. Stimulus intensity was approximately 25 mA, which was relatively comfortable and not too painful for the subjects.

At least 10 successive responses were recorded and superimposed for each side. When onset and end points of ESPs were equivocal, 20 stimuli were recorded and averaged. Only ipsilateral response was considered during analysis. To avoid habituation, a 30s interstimulus interval was given.

The latencies and durations of ESP1 and ESP2 were measured. Sometimes a few muscle activities were seen during ESP2. The EMG activity, not exceeding 20% of maximal amplitude of prestimulus EMG signal was considered as a silent period.

Statistical methods

The comparisons between the electrophysiologic test results of the patients without neurologic signs and healthy control group were performed by *t*-test for independent groups. The neurophysiological test results of the patient subgroups with different types of headache and healthy control group were compared by means of ANOVA and post hoc Tamhane's T2 test or the Kruskal Wallis test, according to the presence or absence of parametric conditions in the related neurophysiological test. Since there was not any ESP2 response on the right in 1 patient and on the left in 8 patients with 'non-structural headache of BD', the remaining latencies of ESP2 were compared using the Kruskall Wallis test.

Table I. The demographic and clinical characteristics of the patients.

	Age (Mean±SD) (years)	Disease duration (Mean±SD) (years)
Whole patients	34.26 ± 10.39	8.05 ± 5.50
Patients with non-structural headache of BD	32.73 ± 9.50	7.82 ± 3.87
Patients with migraine type headache	37.83 ± 10.79	8.57 ± 5.22
Patients with tension type headache	33.27 ± 10.32	10.78 ± 6.77
Patients without headache	33.20 ± 10.57	5.03 ± 4.34

Results

The demographic and clinical characteristics of the patients were shown in Table I.

When BD patients without neurologic signs were compared with the healthy control group with regards to the neurophysiologic test results; right BAEP 1-5 interpeak latency prolongation (p=0.01) and left ESP2 duration shortening (p<0.005) were seen in BD patients. (Table II). In BAEP studies, longer interpeak latencies and in ESP studies, shorter durations indicated a brain stem dysfunction in BD patients.

On comparison among subgroups of BD patients with different types of headache and the healthy control group, the subgroup with non-structural headache of BD was found to have shorter ESP1 and 2 durations (p<0.001 for ESP1 and left ESP2, p=0.001 for right ESP2) and longer ESP1 latencies (p<0.05), with respect to the other patient subgroups with different types of headache and healthy control group, showing brain stem pathology. There was not any ESP2 response on the right in 1 patient and on the left in 8 patients with 'non-structural headache of BD'. Additionally, they had longer right BAEP 3-5 interpeak latency as compared to the patient subgroup without headache (p=0.001) (Table III).

Discussion

In this study, it was found that BD patients without any neurological signs or neuroradiologic (MRI) findings showed neurologic involvement in some neurophysiologic tests studying brain stem primarily. A bilateral frontal, paroxysmal throbbing headache defined as non-structural headache of BD by some authors was found to be related with this neurologic involvement. It seems that this type of headache might be useful to detect the patients with silent neurologic involvement, who were possibly candidates for neuro BD.

Silent neurologic involvement in literature was defined as having minor abnormalities on neurologic examination and/or abnormal findings on neurophysiologic tests on neurologic evaluation performed routinely or due to the complaint of headache. A bilateral frontal, paroxysmal throbbing headache in BD patients was mentioned first by Serdaroglu *et al*. (1). Some BD patients without neurologic attacks and with headache developed neurologic attacks in a seven-year follow-up period in a prospective study (9). Recently, Saip *et al*. (16) called this type of headache 'non-structural headache of BD' and found it commonly associated with mucocutaneous exacerbations of the disease. This headache was frontal, bilateral paroxysmal throbbing pain of moderate severity and did not fulfill the criteria of the International Headache Society for any of the primary headaches. They concluded that it was not specific for BD, but might be explained as a vascular headache triggered by immunomediated disease activity in susceptible individuals. We observed

Table II. The significant neurophysiological test results on comparison of BD patients with healthy control group.

	Patients (n:150)		Healthy controls (n:30)		t	*p*-value
	Mean±SD	Median (Min-max)	Mean±SD	Median (Min-max)		
Right BAEP 1-5 interpeak latency (msec)	4.21 ± 0.49	4.30 (1.38–5.00)	3.95 ± 0.62	3.97 (2.06–4.92)	2.51	=0.01
Left ES1 latency (msec)	11.96 ± 2.69	11.40 (8.80–24.40)	11.49 ± 1.30	11.40 (9.30–14.60)	2.24	<0.05
Left ES2 duration (msec)	33.53 ± 13.09	34.80 (0.00–72.00)	40.07 ± 9.73	41.50 (26.40–63.80)	3.06	<0.005

*SD: Standard deviation.

Table III. The significant electrophysiological test results on comparison among the patient subgroups based on headache type and healthy control group.

	Groups	n	Mean±SD	Median (min-max)	% 95 CI	Statistical evaluation with ANOVA test and posthoc Tamhane T2 test
Right BAEP 3-5 interpeak latency (msec)	1	30	1.87 ± 2.33	1.94 (1.20–2.00)	1.78 ± 1.95	F=5.12, *p*=0.001
	2	30	2.34 ± 0.77	2.22 (1.56–4.50)	2.05 ± 2.63	Group 1 <Group 2 latency
	3	30	1.99 ± 0.31	2.02 (1.10–2.48)	1.87 ± 2.10	
	4	30	2.12 ± 0.30	2.08 (1.50–2.80)	2.00 ± 2.23	
	5	30	2.02 ± 0.31	2.06 (1.40–2.62)	1.90 ± 2.14	
Right ES1 duration (msec)	1	30	15.68 ± 1.21	15.70 (13.00–19.80)	15.24 ± 16.14	F=5.75, *p*<0.001
	2	30	13.77 ± 1.25	18.80 (12.40–18.40)	13.31 ± 14.24	Group 2 <Group 1 duration
	3	30	16.77 ± 3.72	15.10 (12.02–24.00)	15.39 ± 18.16	Group 2 <Group 3 duration
	4	30	16.48 ± 2.85	16.40 (12.60–20.80)	15.41 ± 17.55	Group 2 <Group 4 duration
	5	30	15.57 ± 3.28	15.90 (10.00–19.80)	14.34 ± 16.79	
Right ES1 latency (msec)	1	30	11.60 ± 2.04	11.80 (1.90–14.20)	10.83 ± 12.36	F=2.75, *p*<0.05
	2	30	12.01 ± 1.68	12.75 (8.80–14.00)	11.38 ± 12.63	Group 2 >Group 3 latency
	3	30	10.88 ± 1.17	10.60 (9.00–13.60)	10.44 ± 11.31	
	4	30	11.39 ± 0.77	11.60 (10.00–12.40)	11.10 ± 11.67	
	5	30	11.13 ± 1.12	11.30 (9.00–13.20)	10.71 ± 11.55	
Right ES2 duration (msec)	1	30	43.82 ± 11.93	41.90 (31.00–74.20)	39.37 ± 48.27	F=5.31, *p*=0.001
	2	30	31.82 ± 14.41	35.40 (0.00–80.80)	26.44 ± 37.20	Group 2 <Group 1 duration
	3	30	39.97 ± 8.36	42.90 (25.00–51.00)	36.85 ± 43.10	Group 2<Group 4 duration
	4	30	42.59 ± 5.86	44.40 (33.20–49.40)	40.40 ± 44.78	Group 2<Group 5 duration
	5	30	43.78 ± 16.26	44.00 (27.40–94.00)	37.70 ± 49.85	
Left ES1 latency (msec)	1	30	12.57 ± 4.04	11.10 (10.60–24.40)	11.06 ± 14.08	F=2.90, *p*<0.05
	2	30	12.72 ± 2.78	12.60 (9.00–17.40)	11.68 ± 13.77	Group 2 >Group 3 latency
	3	30	11.59 ± 1.64	11.60 (9.00–14.80)	10.97 ± 12.20	
	4	30	10.97 ± 0.89	11.40 (8.80–11.60)	10.63 ± 11.30	
	5	30	11.49 ± 1.30	11.40 (9.30–14.60)	11.47 ± 12.27	
Left ES2 duration (msec)	1	30	37.85 ± 7.49	41.25 (24.80–51.60)	35.05 ± 40.65	F=23.82, *p*<0.001
	2	30	19.32 ± 14.42	23.50 (0.00–44.40)	13.94 ± 24.70	Group 2<Group 1 duration
	3	30	35.68 ± 9.09	37.00 (19.20–72.00)	32.28 ± 39.07	Group 2<Group 3 duration
	4	30	41.27 ± 7.85	41.40 (29.40–55.60)	38.34 ± 44.20	Group 2<Group 4 duration
	5	30	40.07 ± 9.73	41.15 (26.40–63.80)	36.44 ± 43.70	Group 2<Group 5 duration

*SD:Standard deviation; **CI:Confidence interval; §Group 1: Patient group without headache; Group 2: Patient group with non structructural headache of BD; Group 3: Patient group with migraine type headache; Group 4: Patient group with tension type headache; Group 5: Healthy control group.

that this type of headache was related statistically with silent neurologic involvement detected with electrophysiological tests. An earlier study before the definition of 'non-structural headache of BD' mentioned a relationship between headache and mucocutaneous attacks (20). In this study performed on 118 BD patients, primary headaches of some patients were exacerbated with systemic BD flare-ups; some of these headaches were migraine attacks triggered only by BD activation which showed a good response to the treatment of systemic inflammation. The patients with this headache were investigated extensively, including cranial MRIs and CSF examinations. However, no signs of neurological involvement could be demonstrated. But electrophysiological tests were not applied. In another earlier study performed on 27 BD patients and 27 control subjects, Monestro *et al*. (21) found that 88.9% of BD patients complained of headaches; of these, 50% suffered from migraine without aura. They could not explain

the high frequency of migraine in terms of demographical, clinical, and behavioural variables, probably accounting for a vascular or neuronal subclinical dysfunction. They concluded that as previously evidenced by clinical and neuroimaging reports (9, 22), migraine as the first neurological symptom of BD could herald neurological involvement (21).

In a later case-control study taking the 'non-structural headache of BD' into account performed by Haghighi *et al*. (23), the prevalence and characteristics of different types of headache in BD were investigated. The authors categorised a group of migrainous headache that occurred for the first time with close temporal relationship with evolution of BD as 'BD-induced migraine headache'. They reported BD-induced migraine headache did not differ significantly in most aspects of headache like pulsatility, laterality, accompaniment with nausea, photophobia, phonophobia but reaction to physical activity. Although association with oral aphthae, which was reported to be the most important characteristic of non-structural headache of BD in the literature, tended to be more common in this subgroup of patients with BD-induced migraine headache, this tendency was not found to be at statistically significant level. The study did not consider any neurologic involvement in the patients. In our study, we considered the headache typing of non-structural headache of BD in a different way which did not regard a close temporal relationship with the disease and examined the patients for silent neurologic involvement.

Our study led us to think that headache may be related to neurologic involvement in BD. In a wider view, this might be true for the other vasculitic diseases of CNS like SLE. In 1970s, an intractable headache syndrome distinct for SLE called lupus headache that occurred in the absence of renal dysfunction, hypertension and active CNS involvement was first described. Since then, the importance of headache in SLE has been continued to be argued (24-26).

The neurophysiologic studies of auditory, visual, somatosensory evoked potentials, transcranial magnetic stimulation and brain perfusion SPECT performed on BD patients demonstrated abnormalities providing functional information complementary to imaging studies. It was suggested that the neurophysiologic studies were valuable in monitoring BD activity or therapeutic response and disclosing subclinical CNS involvement (27-30). Tartaroğlu *et al*. (31) studied blink reflex, exteroceptive suppression of masseter and BAEP as brain stem neurophysiologic tests in 37 BD (6 with neuro-BD) patients and found that all of the neurophysiologic tests showed abnormalies in only neuro-BD patients, the most frequently being in exteroceptive suppression period test. In the study, 4 out of 6 patients with neuro-BD showed abnormalities involving ESPs of the masseter (unrecordable in 3 and prolonged latency of ESP2 in 1 patient). In our study, we found both BAEP and ESP abnormalities in the patients without apparent neurologic involvement. The prolongation of BAEP 1-5 interpeak latency showed a pathology in the brain stem in BD without overt neurologic involvement. But this pathology did not seem to be statistically. in correlation with headache We found that ESP1 and ESP2 periods in the patients with non-structural headache of BD were statistically shorter than the other patient groups and healthy control group, showing a pathology related to inhibitory neurons in the brainstem.

In the ESP study, after stimulation of the mental nerve, impulses reach the pons through the sensory mandibular root. The ESP1 response is probably mediated by one inhibitory interneuron, located close to the ipsilateral trigeminal motor nucleus. The inhibitory interneuron projects onto jaw-closing motor neurons bilaterally. The whole circuit lies in the midpons (32). The afferents for ESP2 descend in the spinal trigeminal tract and connect with a polysynaptic chain of excitatory interneurons, probably located in the lateral reticular formation, at the level of the pontomedullary junction. The last interneuron of the chain is inhibitory and gives rise to ipsilateral and contralateral collaterals that ascend medial to the right and left spinal trigeminal complexes to reach the trigeminal motor neurons (32). The ESP1 period appears to be insensitive to peripheral conditioning and suprasegmental modulation, its latency varies little. For these reasons, it is the best available response for assessing lesions along the reflex arc. The ESP2 period is far less sensitive than ESP1 to lesions along the reflex arc. Being mediated by a multisynaptic chain of interneurons of the lateral reticular formation, however, it is modulated by suprasegmental influences (33). The prolongation of ESP latencies and shortening of ESP durations show the pathology of inhibitory neurons in the brain stem, as we have found.

When neurological involvement is present, early diagnosis and treatment is essential in reducing progression of CNS disease (34). The frank onset of neurological involvement commonly occurs 4-6 years after the onset of BD. However, there are some patients with neurological involvement due to BD, prior to the characteristic oral and skin lesions (5). Therefore, it should not be surprising to diagnose a subclinical neurologic involvement in patients with BD. The sensitivity of MRI is not very high in the detection of CNS lesions due to BD (5, 29). Electrophysiologic methods are useful in demonstration of subclinical CNS lesions in BD. In this study, in addition to the electrophysiologic studies, a vascular type headache defined as 'non-structural headache of BD' seems to be possibly related with silent neurologic involvement in BD. This may be an useful and guiding information in the clinical assessment of BD patients if confirmed by other studies, especially prospective ones.

References

1. SERDAROGLU P, YAZICI H, OZDEMIR C, YURDAKUL S, BAHAR S, AKTIN E: Neurological involvement in Behçet's syndrome-a prospective study. *Arch Neurol* 1989; 46: 265-9.
2. ASHJAZADEH N, BORHANI HAGHIGHI A, SAMANGOOIE S, MOOSAVI H: Neuro-Behçet's disease: a masquerader of multiple sclerosis. A prospective study of neurological manifestations of Behçet's disease in 96 Iranian patients. *Exp Mol Pathol* 2003; 74: 17-22.
3. AL-ARAJI A, SHARQUIE K, AL-RAWI Z: Prevalence and patterns of neurological involvement in Behçet's disease: a prospective

study from Iraq. *J Neurol Neurosurg Psychiatry* 2003; 74: 608-13.
4. LACHANPAL S, TANI K, LIE JT, KATOH K, ISHIGATSUBO Y, OHOKUBO T: Pathologic features of Behçet's syndrome: a review of Japanese autopsy registry data. *Hum Pathol* 1985; 16: 790-5.
5. SERDAROGLU P: Behçet's disease and the nervous system. *J Neurol* 1998; 245: 197-205.
6. GHERARDI D: Neurological disorders in Behçet's syndrome. *Lavaro Neuropsichiatr* 1965; 37: 281-8.
7. SHIMIZU T, EHRLICH G, INABA G, HAYSHI K: Behçet disease (Behçet syndrome). *Semin Artritis and Rheum* 1979; 8: 223-60.
8. AHMED F, MAMFORD J, COUGHIE A, CHAMBERLAIN MA, NOBLE B: Neuropsychological impairment in Behçet's disease. *Rev Med Interne* 1993; 14 (Suppl. 1): 40.
9. AKMAN-DEMIR G, BAYKAN-KURT B, SERDAROGLU P *et al*.: Seven year follow-up of neurologic involvement in Behçet syndrome. *Arch Neurol* 1996; 53: 691-4.
10. TUNC R, KEYMAN E, MELIKOGLU M, FRESCO I, YAZICI H: Target organ associations in Turkish patients with Behçet's disease: a cross sectional study by explanatory factor analysis. *J Rheumol* 2002; 29: 2393-6.
11. KRAUSE I, LEIBOVICI L, GUEDJ D, MOLAD Y, UZIEL Y, WEINBERGER A: Disease patterns of patients with Behçet's disease demonstrated by factor analysis. *Clin Exp Rheumatol* 1999; 17: 347-50.
12. HATEMI G, FRESKO I, TASCILAR K, YAZICI H: Increased enthesopathy among Behçet's syndrome patients with acne and artritis: an ultrasonography study. *Artritis Rheum* 2008; 58: 1539-45.
13. ARIDA A, VAIOPOULOS G, MARKOMICHELAKIS N, KAKLAMANIS P, SFIKAKIS PP: Are clusters of patients with distinct clinical expression present in Behçet's disease? *Clin Exp Rhematol* 2009; 27 (Suppl. 53): 48-51.
14. KIDD D: The prevalance of headache in Behçet's syndrome. *Rheumatology* 2006; 45: 621-3.
15. BHAKTA BB, BRENNAN P, JAMES TE, CHAMBERLAIN MA, NOBLE BA, SILMAN AJ: Behçet's disease: evaluation of a new instrument to measure clinical activity. *Rheumatology* 1999; 38: 728-33.
16. SAIP A, SIVA A, ALTINTAS A *et al*.: Headache in Behçet's syndrome. *Headache* 2005; 45: 911-9.
17. INTERNATIONAL STUDY GROUP FOR BEHÇET'S DISEASE: Criteria for diagnosis of Behçet's disease. *Lancet* 1990; 335: 1078-80.
18. HEADACHE CLASSIFICATION SUBCOMMITTEE OF THE INTERNATIONAL HEADACHE SOCIETY: The International classification of headache disorders. *Cephalalgia* 2004; 24 (Supp 1): 1-160.
19. HEADACHE CLASSIFICATION SUBCOMMITTEE OF THE INTERNATIONAL HEADACHE SOCIETY: Classification and diagnostic criteria for headache disorders, cranial nevralgia and facial pain. *Cephalalgia* 1998; 8 (Suppl. 7): 1-96.
20. AYKUTLU E, BAYKAN B, AKMAN-DEMIR G, TOPCULAR B, ERTAS M: Headache in Behçet's disease. *Cephalalgia* 2006; 26: 180-6.
21. MONASTERO R, MANNINO M, LOPEZ G *et al*.: Prevalance of headache in patients with Behçet's disease without overt neurological involvement. *Cephalalgia* 2003; 23: 105-8.
22. AVCI O, KUTLUAY E, ARGON M, ERDEM S, TAHSIN GUNES A: Subclinical cerebral involvement in Behçet's disease: a SPECT study. *Eur J Neurol* 1998; 5: 49-53.
23. BORHANI HAGHIGHI A, AFLAKI E, KETABCHI L: The prevalance and characteristics of different types of headache in patients with Behçet's disease, a case-control study. *Headache* 2008; 48: 424-9.
24. SFIKAKIS PP, MITSIKOSTAS MM, MANOUSSAKIS MN, FOUKANALI D, MOUTSOPOULOS HM: Headache in systemic lupus erythematosus: a controlled study. *Br J Rheumatol* 1998; 37: 300-3.
25. MITSIKOSTAS DD, SFIKAKIS PP, GOADSBY PJ: A meta-analysis for headache in systemic lupus erythematosus: the evidence and the myth. *Brain* 2004; 127: 1200-9.
26. MITSIKOSTAS DD: Is migraine really comorbid with systemic lupus erythematosus? *Cephalalgia* 2004; 24: 1013-5.
27. STIGSBY B, BOHLEGA S, AL-KAWI MZ, AL-DALAAN A, EL-RAMAHI K: Evoked potential findings in Behçet's disease. Brain stem auditory, visual, and somatosensory evoked potentials in 44 patients. *Electroencephalogr and Clin Neurophysiol* 1994; 92: 273-81.
28. NAKAMURA Y, TAKAHASHI M, KITAGUCHI M, IMAOKA H, TARUI S: Brainstem auditory and somatosensory evoked potentials in neuro-Behçet's syndrome. *Jpn J Psychiat Neurol* 1989; 43: 191-200.
29. NAKAMURA Y, TAKAHASHI M, UEYAMA K *et al*.: Magnetic resonance imaging and brainstem auditory evoked potentials in neuro-Behçet's disease. *J Neurol* 1994; 241: 481-6.
30. VIGNOLA S, NOBII F, PICCO P *et al*.: Brain perfusion SPECT in juvenile neuro-Behçet's disease. *J Nucl Med* 2001; 42: 1151-7.
31. TATAROGLU C, KIYLIOGLU N, BICEROL B, SARSU S, TURSEN U, KAYA TI: Exteroceptive suppression of masseter in Behçet's disease. *Journal of neurological sciences* (Turkish) 2005; 22: 250-60.
32. ONGERBOER DE VISSER BW, CRUCCU G, MANFREDI M, KOELMAN JHTM: Effects of brainstem lesions on the masseter inhibitory reflex. Functional mechanisms of reflex pathways, *Brain* 1990; 113: 781-92.
33. CRUCCU G, ONGERBOER DE VISSER BW: The jaw reflexes. *In* DEUSCHL G, EISEN A (Eds). Recommendations for the Practice of Clinical Neurophysiology: Guidelines of the International Federation of Clinical Neurophysiology (2nd Revised and Enlarged Edition). Electroencephalography and Clinical Neurophysiology Supplement no 2, Elsevier Science 1999: 243-7.
34. BESANA C, COMI G, DEL MASCHIO A *et al*.: Electrophysiological and MRI evaluation of neurological involvement in Behçet's disease. *J Neurol Neurosurg Psychiatry* 1989; 52: 749-54.