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ORIGINAL ARTICLE

Peripheral neuropathy in Behçet disease: an electroneurophysiological study

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Abstract The aim of this study was to determine the peripheral nerve involvement electrophysiologically in Behçet patients without clinically evident neurological signs and symptoms. Sixty-three patients who fulfilled the International Study Group Classification Criteria for Behçet's disease (BD) and 49 healthy control subjects were enrolled to the study. Conventional electrophysiological studies of peripheral nerves including F latencies were performed to all subjects. Thirty-one male and 32 female Behçet patients with a mean age of 33.6±11.1 years and (22 male and 27 female healthy control subjects with a mean age of 35.8±9.9 years were included to the study. All but four of the patients were active. In the BD group, electrophysiologically diagnosed neuropathy was detected in nine (14.28%) patients. One (1.58%) patient had sensorimotor polyneuropathy, one patient (1.58%) had sural and ulnar sensorimotor neuropathy, three (4.75%) patients had median and one patient (1.58%) had ulnar sensorimotor neuropathy. Sural nerve sensorial action potential was unobtainable in two (3.17%) patients and prolonged F latencies were observed in two (3.17%) patients. In the control group only one subject (2.4%) had low sural sensorial conduction velocity. The frequency of neuropathy was higher in the patients with BD when compared with the control subjects. Sensory nerves were affected more prominently than motor nerves. There was no relationship between the clinical and laboratory characteristics of the patients and the electrophysiologic findings. No significant difference was observed between the clinical parameters of the patients with and without electrophysiologically detected neuropathy, except the levels of disease duration (8.8±5.1 vs 5.28±4.3 years, respectively, $p<0.05$). In conclusion, Behçet patients may have subclinical peripheral nerve involvement. Conventional electrophysiologic nerve conduction studies including F responses are recommended in routine examination to diagnose early neuropathy in Behçet patients without evident neurologic symptoms.

Keywords Behçet's disease · Electrophysiology · Peripheral neuropathy

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Introduction

Behçet's disease (BD) is a chronic multisystemic disorder described by a Turkish physician "Hulusi Behçet" in 1937 as a triple symptom complex consisting of aphthous ulcers of the mouth and genital and relapsing uveitis [1]. In addition to the characteristic triad, BD commonly involves cardiovascular, pulmonary, articular, gastrointestinal, and neurologic systems, causing a variety of clinical problems [2]. Neurological involvement in BD is heterogeneous and it is a major cause of morbidity [3]. Patients with BD may present with different neurological problems related either directly or indirectly to the disease. The frequency of neurological involvement in BD varies from 2.2 to 49% in large patient series [4–6]. The most common neurological symptoms among patients with BD is headache, followed by weakness of upper motor neuron type, brainstem, and cerebellar and cognitive/behavioral disorders [5, 6]. Periph-

eral nervous system involvement is extremely rare, reported as case reports and in some series, mostly in patients who presented with clinical neurological symptoms [6–9].

The aim of this study was to determine the peripheral nerve involvement electrophysiologically in Behçet patients without clinically evident neurological signs and symptoms.

Materials and methods

Sixty-three patients who were admitted to Behçet follow-up outpatient clinic of Dermatology and 49 healthy control subjects (age and sex matched volunteered hospital staff) were recruited in the study. All patients fulfilled the International Study Group Classification Criteria for BD [10]. Patients with diabetes mellitus, connective tissue disease, kidney, liver, and thyroid diseases, amyloidosis, chronic heart failure, malignancies, and abuse of alcohol were excluded. A complete neurological examination was performed for patients with BD and control group; muscle weakness, paresthesias, hypoestesia, abnormalities of deep tendon reflexes, and vibration threshold were evaluated for assessing peripheral nervous system involvement. Subjects diagnosed to have nervous system diseases and/or patients with neurologic signs or symptoms were not included to the study. Data about demographic characteristics, duration of the disease, and drug intake were obtained. To assess disease activity, the active clinical manifestations of the patients were recorded on the day of the sampling. Each manifestation that was designated to be a criterion for the diagnosis of Behçet disease was scored separately. Additional organ systems that were active in the patient were also scored separately [11, 12]. Levels of erythrocyte sedimentation rate (ESR) by Westergren method and C-reactive protein (CRP) by nephelometric method were measured as laboratory variables in Behçet patients.

Electrophysiological studies were performed to all subjects and the results were assessed according to the American Diabetes Association Diabetic Neuropathy Protocol [13]. Electrophysiological studies were conducted by Nihon Kohden Neuropack 2 EMG device. The temperature of room was maintained at 22–24°C and the temperature of the limbs was kept above 34°C. Median, ulnar, and peroneal nerve motor nerve conduction studies, F waves, and median, ulnar, and sural nerve sensory nerve conduction studies were performed in all subjects using the techniques described by Oh [14]. Orthodromic method was used for the sensory nerve conduction velocities. F responses were determined using surface electrodes placed on the same extremities on which conventional median, ulnar, and peroneal nerve conduction studies were conducted. A series of 20 maximal stimuli at 0.5 Hz frequency and 0.2 ms duration were delivered at the wrist and ankle. Only responses of <20 μV were accepted as actual F responses [15]. All of the electrophysiologic examinations were performed by an experienced psychiatrist. The electromyographer has known the patients' diagnosis but was not aware of the patients' clinical status. Axonal pathology and demyelination of the nerves were described as diminished sensory or compound nerve action potential (SNAP and CNAP, respectively) amplitude and slowing in the conduction velocity of sensory or motor nerves, respectively [14, 15].

Statistical analysis

Demographic properties of the patients, active clinical manifestations, and electrophysiological findings were summarized by descriptive statistics. Chi-square test was used to determine the differences between the frequency of electrophysiological findings of the patient and control groups. Mann–Whitney U test was conducted to evaluate the differences between the clinical parameters of the patients with and without pathological electrophysiologic findings. The relationship between the clinical and laboratory characteristics and the electrophysiological findings of the patients were determined by Spearman correlation analysis. Statistical significance was determined at $p<0.05$. All statistical analyses were performed by SPSS version 11.0 software package.

Results

Sixty-three (31 men and 32 women) Behçet patients with a mean age of 33.6±11.1 years and 49 (22 men and 27 women) healthy control subjects with a mean age of 35.8± 9.9 years were included to the study. There was no significant difference between the patient and control groups in terms of age and gender ($p>0.05$). The demographic and clinical manifestations of BD patients are given in Table 1. All but four of the patients were active. Drug intake of the patients were as follows: all patients were using colchicine and were receiving immunosuppressive therapy (azathiopurine and/or cyclophosphamide); two patients were on acetylsalicylic acid treatment;

Table 1 The demographic and clinical properties of the patients

	Mean±SD (min–max)
Age (years)	33.6±11.1 (18–55)
Duration of disease (years)	5.28±4.3 (1–18)
Number of active system involvement	2.37±1.15 (1–5)
ESR (mm/h)	20.1±12.8 (4–53)
CRP (g/dl)	8.98±4.21 (1–34)

and two patients were taking oral anticoagulation for venous thrombosis.

In BD group, electrophysiologically diagnosed neuropathy was detected in nine (14.28%) patients. One (1.58%) patient had sensorimotor polyneuropathy, one (1.58%) patient had sural and ulnar sensorimotor neuropathy, and three (4.75%) patients had median and one patient (1.58%) had ulnar sensorimotor neuropathy. Sural nerve sensorial action potential was unobtainable in two (3.17%) patients and prolonged F latencies were observed in one (1.58%) patient. In the control group only one subject (2.4%) had low sural sensorial conduction velocity. The frequency of neuropathy was higher in the patients with BD when compared with the control subjects and the difference was statistically significant ($p<0.05$). The distribution of electrophysiologic findings of the patients is shown in Table 2. The electrophysiologic studies indicated demyelination and axonal degeneration in the examined nerves. Sensory nerves were affected more prominently than motor nerves. CMAP or SNAP amplitudes were much more affected than decreased conduction velocity and prolonged distal latency. Patients with electrophysiologically determined neuropathy were all clinically active. Clinical characteristics of BD patients with neuropathy are given in Table 3.

There was no relationship between the clinical and laboratory characteristics of the patients and the electrophysiologic findings. The mean of ESR and CRP values were 20.10 mm/h and 8.98 mg/l, respectively, for all the patients and 20.4 mm/h and 8,98 mg/l for neuropathy group, respectively; there was no significant difference between the neuropathy group and all patients. No significant difference was observed between the clinical parameters of the patients with and without electrophysiologically detected neuropathy, except the levels of disease duration (8.8±5.1 vs 5.28±4.3 years, respectively, $p<0.05$).

Table 2 The distribution of electrophysiologic findings according to number of patients

	Prolonged distal latency (*n*)	Decreased conduction velocity (*n*)	Decreased amplitude (CMAP or SNAP) (*n*)	Prolonged F latency (*n*)
Median motor nerve	3	–	4	1
Median sensory nerve	–	1	4	–
Ulnar motor nerve	3	–	–	–
Ulnar sensory nerve	–	1	2	–
Peroneal motor nerve	–	–	1	1
Sural sensory nerve	–	4	5	–

Discussion

Central nervous system (CNS) involvement of BD is well recognized, but peripheral nerve involvement is a rare complication of BD. Peripheral neuropathy has previously been reported with nerve biopsy and electrophysiological studies commonly as case reports and rarely in some series. Clinically evident peripheral nerve involvement is unusual and has not been reported in large series including 50–200 patients with neurological symptoms [6, 16]. Lannuzel et al. [7] evaluated Behçet patients who were diagnosed with neurological manifestation of BD and reported mostly CNS involvement. Only two patients had peripheral neuropathy characterized as axonal sensory and sensory motor distal polyneuropathy, one of whom had an associated myopathy [7].

Namer et al. [8] described a patient with prominent peripheral nervous system involvement, predominantly axonal damage with evidence of degeneration and regeneration. O'Duffy et al. [17] concluded peripheral neuropathy in lower extremities of their Behçet patients with clinical signs but electrophysiologic studies were not performed. Wakayama et al. described two cases with mononeuritis multiplex, which were diagnosed with electrophysiologic studies. Serdaroğlu et al. [4] investigated the prevalence and type of neurologic involvement in 46 Behçet patients with neurologic symptoms; only one (2.1%) patient had peripheral neuropathy.

Current literature have less detailed information about subclinical peripheral nerve involvement in Behçet patients. In recent years, a growing interest began to enlighten subclinical peripheral nerve involvement in BD but peripheral nervous system research in BD is still in its early stages. There are only two electrophysiologically planned studies evaluating peripheral nerve involvement in BD in the English literature [15, 18]. Birol et al. [18] studied 26 Behçet patients without prominent complaints of neuropathic symptoms and electrophysiologically determined peripheral neuropathy was reported in more than half of their patients. The nerve dysfunction was an axonal type of distal polyneuropathy predominantly involving lower extremities. Budak et al. [15] determined tibial and ulnar motor and sensory nerve, sural nerve conduction studies, and F waves in 30 patients and found no significant difference between the results of Behçet patients and

Table 3 The clinical characteristics of the patients with electrophysiologically determined neuropathy

Sex	AGE	Disease duration	Oral aphthous	Genital ulcer	Ocular involvement	Cutaneous lesion	Pathergy	Vascular	Arthropathy	Neuropathy
M	48	10	+	+	+	−	+	+	−	Polyneuropathy Prolonged F
M	41	10	+	+	+	+	−	−	−	Mononeuritis multiplex
F	40	1	+	+	−	−	+	−	−	Ulnar neuropathy
F	36	10	+	+	−	+	−	−	+	(−) Sural CNAP
F	32	4	+	+	−	+	−	−	−	Median neuropathy
F	35	15	+	−	+	+	−	−	+	Median neuropathy
F	42	8	+	+	−	+	−	−	−	Prolonged F
F	34	5	+	−	+	+	+	−	−	(−) Sural CNAP
F	41	17	+	+	−	+	−	−	−	Median neuropathy

control subjects except for the levels of tibial F responses. The authors concluded that F response parameters are the most sensitive parameters for the detection of mild peripheral neuropathy in patients with BD [15]. In our study, we have performed electrophysiologic studies to 63 Behçet patients and the frequency of subclinical neuropathy was found in 14.2% of patients, lower than in previous studies This may be explained by the selection of patients who were under medical attention and clinical follow-up, with no clinical signs and symptoms of neurologic involvement.

In our study, sensory nerves were affected more prominently than motor nerves while upper and lower extremity nerves were similarly affected, as previously reported [18]. Latencies and conduction velocities of motor nerves were slightly affected and the type of involvement was particularly axonal degeneration. No significant association of electroneuromyographic findings to the activity of BD and ESR and CRP were observed in our study. A lack of correlation between clinical findings and electrophysiologic data was also observed by others [15, 18]. The discrepancy may be related to the subclinical nature of the neurologic dysfunction or the fluctuating characterization of the disease. Electrophysiologically determined peripheral neuropathy was reported mainly in patients with long-standing diseases [18]. In our study, patients who exhibit electrophysiological peripheral neuropathy had a longer disease duration than the patients without peripheral nerve dysfunction, similar to previous data [15, 18].

The effective agents for the treatment of BD, including colchicine, cyclosporine A, azathiopurine, and tacrolismus, may have all neurologic side effects like polyneuropathy and CNS neurotoxicity [19]. All of our patients who exhibited peripheral neuropathy were receiving colchium for BD therapy and one of the patients was on immunosuppressive therapy, but none of them had reported any adverse affects. Also, we did not include patients with neurologic symptoms, therefore, we can exclude the side effects of these treatments.

Electrophysiologic studies used in the evaluation of patients with peripheral neuropathy include conventional sensory and motor peripheral nerve conduction and evaluation of peripheral late responses like F response [20]. The mild to moderate slowing of nerve conduction velocities affecting sensory nerves could represent the first sign of polyneuropathy. F response was recently proposed as an essential technique for detection of mild peripheral neuropathy [15, 20]. The chronodispersion in F response provide information regarding conduction not only in the fastest conduction alpha motor axons but also in relatively slower conduction motor fibers. F response studies indicate the function of the entire course of motor axon so that mild abnormalities in any particular segment can be detected [15]. In our study, we included both conventional peripheral nerve conduction studies and F responses; unlike the previous studies.

The pathophysiology of neuropathy was certainly not explained. Previous authors described this neuropathy as a nonvasculitic axonal neuropathy on nerve biopsies and electrophysiologic studies. Myelin sheaths or axonal bodies might be target neurologic sites for BD's immunopathology [18, 21]. Marked infiltration by neutrophils, eosinophils, and lymphocytes in axons and demyelination was previously reported [19, 22]. There is still a need for further pathophysiologic investigation of peripheral nerves in Behçet disease.

In conclusion, peripheral nervous system may indeed be another site of involvement in patients with BD, even in the absence of neurological signs and symptoms. It is often difficult to diagnose slight or early neuropathy without evident clinical symptoms; therefore, conventional electrophysiologic nerve conduction studies, including F responses may be helpful in the diagnosis of subclinical neuropathy of the patients with BD.

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