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Original Article

An Electrophysiological Study of Peripheral Polyneuropathy in Brucellosis

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Abstract

Background: Brucellosis is an anthroozoonotic disease with heterogeneous clinical presentations. This study aims to investigate the peripheral nervous system (PNS) involvement in brucellosis.

Methods: A total of 57 patients with brucellosis, and 42 age- and gender-matched healthy subjects were enrolled into the study. We performed motor conduction studies that included bilateral median, ulnar, tibial and peroneal nerves, and sensory nerve investigations from bilateral median, ulnar, radial, sural and medial plantar nerves.

Results: Among patients with brucellosis, 21 had neuropathic symptoms. Of these, 9 had abnormalities in nerve conduction studies. The electromyographic testing revealed abnormalities in 2 patients without neuropathic symptoms. Overall, 11 patients (4 males, 7 females) with brucellosis (19.3%) had polyneuropathy (PNP). The mean age of patients with PNP was 52.63 ± 12.06 years, being significantly higher than those without PNP ($P = 0.006$). The mean duration of brucellosis was also longer in patients with PNP, but not significant. The mean distal latency (DL) and nerve conduction velocity (NCV) values were almost always longer in patients with brucellosis than controls, though not statistically significant.

Conclusion: Our results showed that brucellosis causes clinical or subclinical peripheral PNP, and should therefore be considered as a cause of PNP, especially in endemic regions.

Keywords: Brucellosis, electromyography, polyneuropathy

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Introduction

Brucellosis is an endemic anthroozoonotic disease transmitted to humans either by direct contact with infected animals or ingestion of raw meat or unpasteurized milk from such animals.^{1,2} The clinical presentation of brucellosis is heterogeneous as the organism, most widely *Brucella mellitensis*, can involve many organs and tissues. In acute infection, neurological symptoms are common and non-specific such as headache, fatigue or myalgia.¹⁻³ Direct involvement of the central or peripheral nervous system (PNS), on the other hand, is uncommon and may cause life-threatening neurological complications including meningitis, encephalitis, myelitis, polyradiculitis or cranial neuropathy.¹⁻⁵ Polyneuropathy (PNP) due to brucella infection has newly been reported.^{6,7} In this study, we aim to investigate PNS involvement in patients with brucellosis.

Patients and Methods

This prospective study was conducted in the city of Iğdir, an under-developed small city in Eastern Turkey with three international borders to Armenia, Republic of Azerbaijan, and Iran. During six months of the study period, all patients newly diagnosed

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with brucellosis (acute or subacute stages) by the detection of specific antibodies in their blood by standard tube agglutination testing (at a titer of 1: 160 or a 4-fold or greater rise within three weeks)³ were consulted and evaluated by the same neurologist (G.B.). None of the patients presented with neurological symptoms, but they were all referred from internal medicine clinics, and had been examined for brucellosis due to various symptoms such as fatigue, fever, nausea, loss of appetite and weight, generalized myalgia or articular problems. The clinical assessment involved the age and gender of patients, duration of symptoms, past medical history and neurological examination. None of the patients had symptoms that suggested central nervous system involvement. All patients had detailed laboratory analyses that included HbA1c, sedimentation, C-reactive protein, vitamin B12 levels, thyroid function tests, markers for other infections (such as syphilis and HIV) and vasculitis (such as antinuclear antibodies). Patients with any other infectious, metabolic, neurological, rheumatological or musculoskeletal disorders were excluded. None had a history of toxic exposure. We did not perform cerebrospinal fluid analysis, as none had symptoms and/or findings suggestive of central nervous system involvement. Immunoelectrophoresis or immunofixation was not tested; though, serum immunoglobulin levels were within normal limits. None of the patients were given any treatment for brucellosis during the study protocol.

Neuropathic symptoms and signs were investigated for muscle weakness, atrophy, loss of deep tendon reflexes (DTR), positive sensory symptoms (paresthesias, dysesthesias, or cramp-like sensations), negative sensory symptoms (hypoesthesias or anesthesias), pain (allodynia, burning or cutting pain) and loss of deep sensations (pressure, position or vibratory sense).

Table 1. Neurological assessment of patients with brucellosis.

Symptoms (reported on questioning)	Number (%)
Any neuropathic symptom	21 (36.8)
Muscle weakness	8 (14.0)
Sensorial symptoms	16 (28.0)
Signs	
Generalized muscle weakness	2 (3.5)
Atrophy	0 (0)
Decreased deep tendon reflexes (DTR)	4 (7.0)
Dysesthesia	10 (17.5)
Superficial sensory loss	6 (10.5)
Deep sensory loss	0 (0)

Table 2. Differences in electromyographic parameters of brucellosis patients with or without peripheral neuropathy (PNP) and controls.

EMG parameters	Patients with brucellosis		P-value*	Controls (n = 42)	P-value#	P-value [§]
	PNP present (n = 11)	PNP absent (n = 46)				
Tibial nerve, distal latency (ms)	5.2 ± 4.0	5.6 ± 1.3	0.093	5.1 ± 1.3	0.096	0.564
Tibial nerve, amplitude (μV)	7.2 ± 4.3	9.2 ± 4.3	0.276	9.5 ± 3.5	0.130	0.922
Tibial nerve, velocity (m/s)	35.8 ± 16.0	45.3 ± 4.7	0.036	41.9 ± 9.9	0.065	0.368
Tibial nerve, F wave latency (ms)	55.4 ± 7.2	52.4 ± 4.8	0.165	55.2 ± 7.4	0.996	0.226
Peroneal nerve, distal latency (ms)	4.8 ± 3.0	5.0 ± 1.0	0.371	5.0 ± 1.4	0.251	0.342
Peroneal nerve, amplitude (μV)	1.5 ± 0.9	2.3 ± 1.4	0.112	2.1 ± 1.5	0.264	0.458
Peroneal nerve, velocity (m/s)	42.6 ± 16.2	54.6 ± 5.6	0.002	52.8 ± 10.1	0.044	0.624
Peroneal nerve, F wave latency (ms)	47.0 ± 6.0	46.2 ± 5.8	0.461	45.9 ± 3.4	0.655	0.441
Median nerve, distal latency (ms)	4.1 ± 1.7	3.7 ± 0.7	0.050	3.2 ± 0.5	0.036	0.128
Median nerve, amplitude (μV)	7.2 ± 3.3	9.2 ± 4.0	0.049	11.4 ± 3.1	0.050	0.196
Median nerve, velocity (m/s)	58.1 ± 5.2	63.3 ± 5.3	0.001	61.8 ± 3.8	0.028	0.272
Median nerve, F wave latency (ms)	24.8 ± 3.6	24.0 ± 2.4	0.540	23.2 ± 1.8	0.682	0.662
Ulnar nerve, distal latency (ms)	3.1 ± 0.6	2.7 ± 0.3	0.050	2.2 ± 0.2	0.035	0.345
Ulnar nerve, amplitude (μV)	9.5 ± 2.7	9.8 ± 2.5	0.503	13.6 ± 3.0	0.063	0.098
Ulnar nerve, velocity (m/s)	59.0 ± 7.3	64.2 ± 4.1	0.032	63.9 ± 2.1	0.052	0.643
Ulnar nerve, F wave latency (ms)	26.4 ± 2.0	24.8 ± 1.4	0.001	24.8 ± 1.6	0.684	1.000
Sural nerve, latency (ms)	3.9 ± 1.1	2.6 ± 0.4	<0.001	2.3 ± 0.4	<0.001	0.614
Sural nerve, amplitude (μV)	2.8 ± 6.9	16.6 ± 1.6	<0.001	19.4 ± 4.8	<0.001	1.000
Medial plantar nerve, latency (ms)	2.8 ± 0.5	2.2 ± 0.1	0.036	1.9 ± 0.2	0.020	0.435
Medial plantar nerve, amplitude (μV)	6.0 ± 3.4	7.6 ± 6.2	0.042	12.1 ± 2.8	0.004	0.068
Median sensory nerve, latency (ms)	2.9 ± 1.3	2.4 ± 0.5	0.043	2.5 ± 0.7	0.050	0.835
Median sensory nerve, amplitude (μV)	13.7 ± 10.5	21.0 ± 11.8	0.005	30.6 ± 8.9	<0.001	1.000
Ulnar sensory nerve, latency (ms)	1.8 ± 0.9	2.1 ± 0.2	0.050	2.2 ± 0.2	0.045	0.894
Ulnar sensory nerve, amplitude (μV)	10.6 ± 9.6	22.2 ± 12.8	0.003	28.3 ± 10.5	<0.001	0.990
Radial sensory nerve, latency (ms)	2.3 ± 0.6	1.9 ± 0.1	0.052	1.9 ± 0.1	0.056	1.000
Radial sensory nerve, amplitude (μV)	4.3 ± 1.8	12.5 ± 1.9	0.003	24.4 ± 9.3	<0.001	0.038

P-value* for comparisons between brucellosis patients with and without PNP; P-value# for comparisons between patients with brucellosis and PNP and controls; P-value[§] for comparisons between brucellosis patients without PNP and controls.

The electrophysiological evaluation was assessed with patients relaxed in a supine position. All procedures were explained to the subjects before testing. A five-channel electromyography (EMG) apparatus (Myoquick, Bilkosin) was used in testing and calibrated before each data collection. Frequency interval, sweep time and sensitivity were adjusted as 20 Hz–5 kHz, 50 ms–200 ms/div, and 200–1000 μV/div, respectively. Motor conduction studies were performed from bilateral median, ulnar, tibial and peroneal nerves by using supramaximal percutaneous stimulation with surface electrode recording, and the needle EMG was performed in one distal muscle (tibialis anterior, or gastrocnemius). The amplitudes of compound muscle action potentials (CMAP, baseline to the negative peak), distal latencies (DL, from stimulus to initial deflection) were recorded with standard methods, and nerve conduction velocities (NCV, distance divided by proximal latency minus DL) were calculated. Sensory nerve action potentials (SNAPs) were measured by using bar electrodes following orthodromic stimulation from bilateral median, ulnar and radial nerves, and antidromic stimulation for bilateral sural and medial plantar nerves

in terms of DL and amplitude. The presence of PNP was based on EMG findings.⁸

As a control group, we included age- and gender-matched healthy volunteer subjects with no history of brucellosis or any other neurological, rheumatological, musculoskeletal or metabolic diseases that could interfere with the nerve conduction studies. The tube agglutination testing for brucella, as well as all other blood tests performed in patient group were negative in all healthy participants. None of the control subjects had a history of toxin exposure. The study protocol was approved by the institute's Committee on Human Research, and all participants gave their informed consent.

The data was analyzed using the SPSS 12.0 software (SPSS Inc., Chicago, IL, USA). In the statistical analysis, the Chi-square test was used to compare the distribution of categorical variables between groups and the student's *t*- or Mann-Whitney U tests were used to compare continuous variables, as appropriate. As there are many variables involved in the study, one-way ANOVA was performed with *post-hoc* analysis of multiple correlations with

Bonferroni correction. Continuous variables were given as mean \pm standard deviation or percentiles. The threshold of significance was determined at a *P*-value equal to or less than 0.05.

Results

A total of 57 patients with brucellosis and 42 healthy subjects enrolled in the study. The mean age of patients with brucellosis was 42.35 ± 16.46 years and the mean age of control group was 39.75 ± 14.93 years (*P* = 0.556). Of patients with brucellosis, 56.1% were females and 43.9% were males, whereas 57.2% of control subjects were females and 42.8% were males (*P* = 0.862).

Among patients with brucellosis, 21 (36.8%) had neuropathic symptoms upon clinical assessment. Neurological symptoms of patients with brucellosis (reported on questioning) and signs observed upon neurological examination are given in Table 1. Nine (42.8%) out of 21 patients with neuropathic symptoms had abnormalities in nerve conduction studies. The nerve conduction studies were normal in the remaining 12 patients, while 2 (5.5%) patients without any neuropathic symptoms (*n* = 36) had abnormal nerve conduction studies (*P* = 0.001). Overall, 11 patients (4 males, 7 females) with brucellosis (19.3%) had peripheral PNP. The mean age of these patients with PNP was 52.63 ± 19.06 years, being significantly higher than those without PNP (*P* = 0.006). The gender was similar between both groups. The mean duration of brucellosis symptoms was longer in patients with PNP, but not significant (4.2 ± 2.9 versus 3.7 ± 2.3 months, *P* = 0.314). Patients with brucellosis and PNP had significantly longer mean DL and significantly slower mean NCV for motor nerve studies, compared to patients with brucellosis but no PNP (Table 2). The mean CMAP values, however, did not differ between the two groups. The mean latencies for F wave were similar in the two groups. In patients with brucellosis, those associated with PNP and those without PNP. The needle EMG testing revealed that only in 3 (27.2%) with PNP had denervation potentials in the tibialis anterior or gastrocnemius muscle. In sensory nerve analysis, both the mean latency and amplitudes were significantly affected in patients with brucellosis and PNP in compared to those without PNP (Table 2).

The comparisons of electrophysiological parameters in patients with brucellosis and control subjects showed that the mean DL values in patients with brucellosis were almost always longer than those in controls, but not significant (Table 2). The mean NCV values were also longer in patients with brucellosis in compared to controls, although this difference did not reach statistical significance. The differences in the mean CMAP values between patients with brucellosis and control subjects were variable (Table 2).

Discussion

In this study, we observed that peripheral PNP was present in 19.3% of patients with brucellosis, and age was the only risk factor for the development of PNP. In nerve conduction studies, the most prominent finding was the axonal involvement in sensory nerves in patients with brucellosis and PNP, in addition to mild conduction abnormalities in sensory and motor nerves. On the other hand, the comparison of electroneurophysiologic parameters with the age- and gender-matched control group failed to show any significant differences, although longer DL and slower conduction velocities were noticed in patients with brucellosis.

In the literature, mild demyelinating sensorial PNP was reported

in one patient with brucellosis, which disappeared one month after successful treatment.⁶ The other study that has investigated peripheral PNP caused by brucellosis was a prospective electrophysiological study of 34 patients which reported that 12 patients (35.3%) had sensorimotor axonal peripheral PNP.⁷ In the same study, the authors have found no statistical differences in terms of age, gender and duration of symptoms between patients with and without peripheral PNP, although a trend was noticed towards older age and longer disease duration in patients with PNP. In our study, the frequency of PNP in brucellosis was 19.3% and PNP was observed mainly as axonal sensorial PNP, though mild conduction abnormalities were also observed in sensory and motor nerves. We observed that patients with brucellosis and PNP were significantly older than those without PNP. Although we did not perform EMG studies after treatment for brucellosis as a limitation of our study, in the absence of other risk factors for PNP, we may suggest that brucella organisms be considered as a potential cause for peripheral PNP, especially in endemic areas.

The pathogenesis of PNS involvement in brucellosis is yet not known. Brucella organisms are capable of prolonged intracellular survival within phagocytes and may influence PNS.² It has been suggested to be via direct invasion of the organism and their endotoxins on the peripheral nerve for the axonal-type PNP, or via the immune-mediated mechanisms for demyelinating processes.^{2,4,9} However, it is still unknown how the bacteria causes peripheral nerve dysfunction; additional investigation is warranted.

In present study, the most prominent finding was axonal involvement in sensory nerves in patients with brucellosis and PNP, in addition to mild conduction abnormalities in sensory and motor nerves. Although the pathogenesis of PNS involvement in brucellosis is yet not known, direct invasion of the organism and their endotoxins on the peripheral nerve, or immune-mediated mechanisms could be responsible. In conclusion, Brucellosis should therefore be considered as a cause of PNP, especially in endemic regions.

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