MAJOR ARTICLE

Neurobrucellosis: Clinical and Diagnostic Features

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Background. We describe the neurological involvement in brucellosis and revisited diagnostic criteria for neurobrucellosis.

Methods. Patients with laboratory-confirmed brucellosis who were consequently hospitalized were observed prospectively in a brucellosis-endemic region. The neurobrucellosis was diagnosed by any one of the following criteria: (1) symptoms and signs consistent with neurobrucellosis; (2) isolation of *Brucella* species from cerebrospinal fluid (CSF) and/or presence of anti-*Brucella* antibodies in CSF; (3) the presence of lymphocytosis, increased protein, and decreased glucose levels in CSF; or (4) diagnostic findings in cranial magnetic resonance imaging or CT.

Results. Lumbar puncture was performed in 128 laboratory-confirmed brucellosis cases who had neurological symptoms and signs, and 48 (37.5%) were diagnosed as neurobrucellosis. The sensitivity of tube agglutination (TA) in CSF was 0.94, specificity 0.96, positive predictive value 0.94, and negative predictive value 0.96. *Brucella* bacteria were isolated from CSF in 7 of 48 patients (15%). The mean age of 48 neurobrucellosis patients was 42 years (SD, 19 years), and 16 (33%) were female. The most common neurological findings were agitation (25%), behavioral disorders (25%), muscle weakness (23%), disorientation (21%), and neck rigidity (17%). Cranial nerves were involved in 9 of 48 patients (19%). One patient was left with a sequela of peripheral facial paralysis and 2 patients with sensorineural hearing loss.

Conclusions. Patients with severe and persistent headache and other neurologic symptoms and signs should be considered for neurobrucellosis in endemic regions and to possibly receive longer therapy than 6 weeks. *Brucella* TA with Coombs test in CSF is sensitive and specific by using a cutoff of ≥1:8.

Keywords. neurobrucellosis; clinical; diagnosis; epidemiology.

Brucellosis is a common zoonotic infection in many parts of the world including the Mediterranean and Middle Eastern countries. Turkey is one of the endemic countries for brucellosis [1, 2]. The disease is caused by the bacterial genus *Brucella*. Brucellosis is transmitted to humans by direct contact with infected animals, through cuts and abrasions or inhalation of aerosols, or by ingestion of unpasteurized milk or milk products [1, 3]. Human brucellosis is a multisystem disease that may present with a broad spectrum of clinical manifestations [4].

Neurobrucellosis may develop at any stage of disease and may have widely variable manifestations, including encephalitis, meningoencephalitis, radiculitis, myelitis, peripheral and cranial neuropathies, subarachnoid hemorrhage, and psychiatric manifestations [1, 2, 5]. In the literature, diagnostic criteria of neurobrucellosis is problematic. According to some

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authors, the diagnosis of neurobrucellosis might be based on clinical neurological symptoms, whereas according to some other authors the diagnosis is based on microbiological and/or biochemical evidence from cerebrospinal fluid [6–10]. We aimed to shed light to the obscure areas of diagnosis in neurobrucellosis and have detailed general and neurologic features of our large number of cases as well as their laboratory findings.

METHODS

Study Population

The Ankara Numune Training and Research Hospital (ANTRH) is a 1100-bed referral and tertiary care community hospital in Turkey. This prospective observational study was performed in the Infectious Diseases and Clinical Microbiology Clinic of ANTRH between February 2002 and March 2005. Patients >16 years of age with laboratory-confirmed brucellosis who were consequently hospitalized were included in the study and evaluated for neurologic involvement.

Demographic data, history, physical examination, laboratory results, antibiotic treatment, and follow-ups were recorded on individual structured patient forms. Informed consents were obtained from the patients for lumbar puncture.

Clinical Assessment and Definitions

The diagnosis of brucellosis was based on consistent clinical findings and a serum agglutinin titer of ≥1:160 in serum tube agglutination (STA) or a positive blood culture. All patients were examined for neurological and psychological disorders, and lumbar puncture was performed in patients who had any of the following complaints: severe and persistent headache that prevented the patient's daily activities, insomnia, amenorrhea, incontinence, and clinical findings such as neck stiffness, confusion, depression, changes in personality, and any neurological manifestations. To reach more stringent definition of neurobrucellosis, suspected neurobrucellosis cases were consulted by specialists in neurology, ophthalmology, and psychiatry. Audiometric studies and visual field tests were also performed, if possible.

Neurobrucellosis among laboratory-confirmed brucellosis patients was diagnosed by the presence of any 1 of the following criteria: (1) symptoms and signs suspect of neurobrucellosis, which were described above; (2) isolation of *Brucella* species from cerebrospinal fluid (CSF) and/or presence of anti-*Brucella* antibodies in CSF; (3) the presence of lymphocytosis, increased protein, and decreased glucose levels in the CSF; or (4) findings in cranial magnetic resonance imaging (MRI) or computed tomography (CT). Patients who had only low titers of tube agglutination (TA) in CSF but none of the above criteria were excluded from the group of neurobrucellosis.

Neurobrucellosis was treated primarily by different combinations of ceftriaxone (2 g intravenously twice daily) and rifampicin (600 mg/day orally) and doxycycline (100 mg orally twice daily) for at least 4 months. In some cases, ciprofloxacin, trimethoprim-sulfamethoxazole, and streptomycin were also given as a secondary line of treatment.

Microbiological Studies

Cerebrospinal fluid was tested by serial tube dilution from 1:4 to 1:512 by TA and then by Coombs test for incomplete *Brucella* antibodies. Blood and CSF cultures were analyzed using an automated system (Organon Tecnica BacT/Alert bioMérieux). In biochemical examination of CSF, protein and glucose were measured. The cells in CSF were counted by Thoma cytometer slide.

Statistical Analysis

Data were analyzed by Stata statistical software, version 11.0 (StataCorp). For the comparison of categorical data, χ^2 test was used. The sensitivity, specificity, and positive and negative predictive values of TA in CSF were calculated by setting the cutoff ≥1:8. A receiver operating characteristic (ROC) curve was constructed and the area under the curve was calculated. Statistical significance was set at $P < .05$.

RESULTS

Lumbar puncture was performed and CSF was obtained from 128 patients who had any neurological symptoms and signs described above. Of 128 patients, 48 (37.5%) were diagnosed with neurobrucellosis according to diagnostic criteria (Table 1). Forty-five of 48 (94%) neurobrucellosis patients had an CSF agglutination titer of ≥1:8 . *Brucella* bacteria were isolated from CSF in 7 of 48 patients (15%), and *Brucella* bacteria were also isolated from blood in 5 of these 7 patients. The median number of blood cultures was 6 (range, 3–9). In 2 patients, although no agglutination was detected, *Brucella* bacteria was isolated from CSF. In 28 of 48 neurobrucellosis patients (58%), CSF protein level was >45 mg/dL; in 16 of 48 patients (33%), CSF/blood glucose ratio was <0.4; and in 28 of 48 patients (58%), leukocytes that were mainly lymphocytes were counted in CSF. Thirteen of the 48 patients (27%) diagnosed with neurobrucellosis had findings consistent with neurobrucellosis in cranial MRI and/or CT. Leptomeningeal contrast enhancement was detected in 8 (17%) patients, suspicious nodular lesions in 4 (8%) patients, and granulomatous lesions in 2 (4%) patients. Diagnostic findings for neurologic involvement according to different titers of TA in CSF are depicted in Table 1.

Among patients with neurobrucellosis, 16 (33%) were female and the median age was 42 years (range, 13–77 years);

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Table 1. Diagnostic Findings of 48 Cases of Neurobrucellosis

CSF *Brucella* Agglutination Titer With Coombs Serum	No. of Cases (n = 48)	*Brucella* spp Isolated in Blood Culture (n = 19)	*Brucella* spp Isolated in CSF Culture (n = 7)	CSF Protein >45 mg/dL (n = 28)	CSF/Blood Glucose Ratio <0.4 (n = 16)	Presence of Cells (>5/mm^3) in CSF (n = 28)	MRI/CT Findings Supporting Diagnosis (n = 13)
0	2	2	2	0 (0)	1 (50%)	1 (50%)	0
1/4	1	. . .	. . .	1 (100)	0	0	1 (100%)
1/8	7	4	. . .	4 (50)	0	4 (57%)	3 (42%)
1/16	8	3	1	5 (63%)	2 (25%)	6 (75%)	2 (25%)
1/32	13	3	1	6 (46%)	1 (8%)	6 (46%)	0
1/64	4	1	1	3 (75%)	2 (50%)	4 (100%)	1 (25%)
1/128	2	1	. . .	1 (50%)	1 (50%)	1 (50%)	1 (50%)
1/256	3	1	. . .	2 (66%)	3 (100%)	2 (67%)	2 (67%)
1/512	8	4	2	6 (75%)	6 (75%)	4 (50%)	3 (37%)

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging.

32 patients (65%) raised livestock. The most common route for transmission of infection was consumption of cheese produced from unpausterized milk, which was reported by 41 patients out of 48 (85%). In 8 patients (17%), brucellosis was reported among the family members. In 29 of 48 (60%) neurobrucellosis cases, the symptoms were shown in <2 months.

The most common presenting symptoms and signs are presented in Table 2 and Table 3. Involvement of cranial nerves were detected in 9 of 48 patients (19%): vestibulocochlear in 5 patients, abducens in 2 patients, and facial in 2 patients. In addition, radiculopathy was detected in 6 patients. Audiometric tests could be performed among 30 neurobrucellosis patients, and vestibulocochlear cranial nerve involvement was detected in 5 patients. Two of 5 patients had loss of hearing, and 3 patients were cured according to audiometric tests. A visual field test was performed in 30 neurobrucellosis patients; in 1 patient concentric restriction was detected and became normal after treatment. Electroencephalography (EEG) could be performed among 30 patients; in 6 patients (20%)

Table 2. Presenting Symptoms

Symptom	Neurobrucellosis, No. (%) (n = 48)	Non-neurobrucellosis, No. (%) (n = 80)	*P* Value
General symptoms			
Fever	38 (79)	62 (78)	.825
Myalgia	37 (77)	67 (84)	.350
Sweating	35 (73)	63 (79)	.451
Low back pain	31 (65)	39 (49)	.081
Weight loss	30 (63)	42 (53)	.270
Fatigue	28 (58)	47 (59)	.963
Loss of appetite	26 (54)	33 (41)	.156
Arthralgia	23 (48)	43 (54)	.523
Vomiting	14 (29)	14 (21)	.311
Amenorrhea	1 (2)	2 (1)	.707
Neurologic symptoms			
Headache	41 (85)	51 (64)	.008
Blurred vision	11 (23)	6 (8)	.013
Loss of hearing	9 (19)	4 (5)	.013
Confusion	5 (10)	1 (1)	.018
Incontinence	4 (8)	2 (3)	.131

Table 3. Neurological Signs

Neurological Sign	Neurobrucellosis, No. (%) (n = 48)	Non-neurobrucellosis, No. (%) (n = 80)	*P* Value
Behavioral changes within last month	29 (60)	10 (13)	<.001
Agitation	12 (25)	8 (10)	.024
Muscle weakness	11 (23)	3 (4)	.001
Disorientation	10 (21)	3 (4)	.002
Neck rigidity	8 (17)	2 (3)	.004
Changes in deep tendon reflexes	5 (10)	1 (1)	.018
Paresthesias	5 (10)	1 (1)	.018
Apathy	4 (8)	2 (3)	.131
Dysarthria	3 (6)	1 (1)	.115
Diplopia	2 (4)	0 (0)	.066
Ataxia	2 (4)	0 (0)	.066
Pseudotumor cerebri	2 (4)	0 (0)	.066
Facial paralysis	2 (4)	0 (0)	.066
Areflexia	2 (4)	0 (0)	.066

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nonspecific changes were detected. All these EEG changes disappeared after treatment.

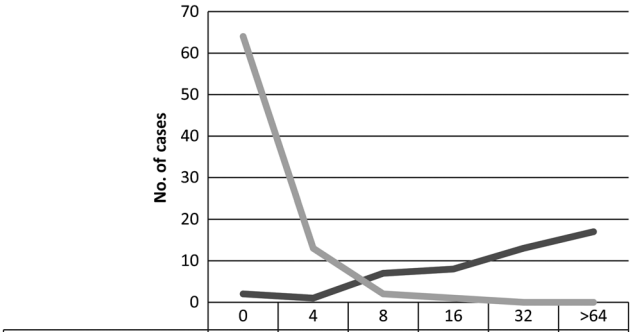
Forty-six of 48 (95%) neurobrucellosis patients were seen by a physician at least once since the onset of symptoms. Before admission to our clinic, 65% of the patients were seen by internal medicine specialists, 16% by neurosurgeons, 10% by physical medicine and rehabilitation specialists, 6% by orthopedicians, and 4% by psychiatrists. Before the admission, 20 of 48 (42%) patients received nonspecific antibiotic therapy, and 9 (19%) had a history of brucellosis treatment.

Treatment and Outcome of the Patients

Thirty-nine of 48 patients (81%) diagnosed with neurobrucellosis received treatment with ceftriaxone (2 g twice daily intravenously) and rifampicin (600 mg/day orally) for 3 weeks and continued with rifampicin (600 mg/day) and doxycycline (100 mg twice daily orally) for a total of 6 months. Nine patients (18%) received rifampicin (600 mg/day orally) and doxycycline (100 mg twice daily orally) for 6 months. After therapy, patients were followed for 3, 6, and 9 months, and no relapse was detected. Of 48 patients, 1 (1.4%) died of cardiac and cerebrovascular illness on the third day of treatment. Three patients with cranial nerve involvements (facial paralysis in one patient, sensorineural hearing loss in 2 patients) recovered with sequelae.

Test Performance of Agglutination Test

Among the patients in whom lumbar puncture was performed, 48 were diagnosed with neurobrucellosis, whereas 80 were not. Among non-neurobrucellosis cases, 16 of 80 (20%) had low level of agglutination positivity in CSF (Figure 1).



	0	4	8	16	32	>64
neurobrucellosis	2	1	7	8	13	17
non-neurobrucellosis	64	13	2	1	0	0

Figure 1. Tube agglutination test results from cerebrospinal fluid (CSF) among 80 brucellosis and 48 neurobrucellosis cases in which lumbar puncture was performed. Two patients with tube agglutination (TA) titer of 1:8 and 1 patient with TA titer of 1:16 in CSF did not have any one of the criteria for neurobrucellosis, and accordingly were not included in the neurobrucellosis group.

Thirteen of 80 non-neurobrucellosis cases had TA titer of 1:4 in CSF with the median serum TA of 1280; 2 cases had TA titer of 1:8 in CSF with an STA of 1280 and 320, and 1 patient had a TA titer of 1:16 in CSF with an STA of 10 240. Two patients with a TA titer of 1:8 and 1 patient with a TA titer of 1:16 in CSF did not have any of the criteria for neurobrucellosis and were accordingly not included in the neurobrucellosis group.

The ROC curve of true neurobrucellosis cases against false-positive neurobrucellosis cases was plotted according to TA in CSF. With the threshold of 1:8 of TA in CSF, the sensitivity of the agglutination test was found to be 0.94 (95% confidence interval [CI], .83–.99), specificity was 0.96 (95% CI, .89–.99), positive predictive value was 0.94 (95% CI, .83–.99), and negative predictive value was 0.96 (95% CI, .89–.99). By defining the threshold as 1:8, the area under the ROC curve was found to be 0.95 (95% CI, .91–.99).

DISCUSSION

Neurobrucellosis is an important complication of systemic brucellosis infection [1, 5]. It is a historically significant disease that might have been the cause of the chronic and severe headaches of Florence Nightingale [11]. We present a large series of patients with neurobrucellosis focused on a detailed description of observed neurological features and laboratory findings. In our study period between 2002 and 2005, a total of 65 245 brucellosis patients with a morbidity rate of 20 per 100 000 and a mortality rate of 1 per 1 000 000 were reported by the Ministry of Health of Turkey [12]. The hospital where this study was performed provides the healthcare for the entire population, even those with no health insurance, in the high-endemicity region of the country.

This study was done in the framework of a large population of patients with brucellosis, using lumbar puncture in patients with suspected findings of neurobrucellosis, including severe and persistent headache. The frequency of neurobrucellosis has been reported as 0.5%–25% in the literature [13, 14]. The reasons for the high prevalence of neurobrucellosis cases in our study could be (1) being a reference hospital and having more complicated brucellosis cases from an endemic region, (2) performing the study among hospitalized brucellosis patients, who were severely ill, (3) detailed evaluation for neurological involvement and high rate of lumbar puncture, and (4) having underreported neurological involvements in *Brucella* infections in the literature.

The clinical presentation of central nervous system involvement varies and reported as nonpathognomonic in some studies [1, 5, 13, 15–19]. Headache and depression were reported as only neurologic symptoms in previous studies [5, 7]. In our study, the presence of headache was significantly higher in

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neurobrucellosis cases (85%) than in non-neurobrucellosis cases (53%) ($P < .001$; Table 2). Besides headache, blurred vision, loss of hearing, and confusion were found to be significantly more common among neurobrucellosis patients. Some behavioral and neuropsychiatric disorders such as sleeping disorders, epilepsy, agitation, and depression were reported in neurobrucellosis cases [5, 7, 13, 20]. In our study, behavioral changes within the last month, agitation, muscular weakness, disorientation, neck rigidity, changes in deep tendon reflexes, and paresthesias were found to be significantly more common among neurobrucellosis cases (Table 3). The Mini-Mental State Examination test and the Hamilton depression rating scale also applied to 34 of 48 neurobrucellosis patients, as has been presented in another report [6]. Significant cognitive and emotional improvements were observed by antibiotic therapy, without any antidepressive or antipsychotic therapy [6]. None of our cases had history of epilepsy, but in 6 of 30 patients (20%), nonspecific EEG findings were recorded. All of these EEG abnormalities became normal after treatment. Abducens, facial, and vestibulocochlear cranial nerves were affected more than other cranial nerves in neurobrucellosis [5, 7, 13, 21]. Our results were found to be compatible with these reports. Peripheral nerve involvement may occur as radiculopathy or polyradiculopathy in brucellosis cases [5, 13, 21], and in our study radiculopathy was detected in 6 neurobrucellosis patients. Neurological complications may develop in any stage of brucellosis [15, 22]. Diagnosis of neurobrucellosis is usually made 2–12 months after the onset of symptoms in most cases [9, 20].

In our study, *Brucella* species isolation from the CSF (15%) was found to be in parallel with the isolation rate reported in previous studies of >30% in neurobrucellosis [1, 21, 23]. Because the isolation rate of *Brucella* species from CSF is so low, most of the neurobrucellosis cases were diagnosed by serological methods. In 2 patients with neurobrucellosis, *Brucella* species were isolated from CSF, but no agglutination was detected in CSF, as was reported previously as a case report [24]. Agreement on the diagnostic antibody titer in CSF for neurobrucellosis has not been reached. Diagnostic agglutination titer in CSF was reported as ≥1:80 in 2 studies [22, 25], whereas any titer detected in CSF was accepted as diagnostic in some other studies [7, 9, 15, 20, 23, 26]. The TA test is still widely used worldwide, although enzyme-linked immunosorbent assay (ELISA) could be more sensitive. In a study from Turkey, diagnostic performance of STA and ELISA in brucellosis were found to be similar [27].

As the titers of STA increase, low titers of TA in CSF could be detected, perhaps because of increased permeability of the blood-brain barrier to immunoglobulins, or immunoglobulins produced locally as a response to infectious agents or autoantigens [26]. Previously it was reported that passive antibody transfer alone can account for CSF/serum antibody titer ratios of 1:369 by the STA and Coombs [20, 28]. In our study, TA positivity in CSF was detected in 16 of 80 (20%) non-neurobrucellosis cases and the low level of TA in CSF in patients with high titer of STA is depicted in Figure 1. In this study, we excluded 3 patients, who had only low titers of TA in CSF but who did not have one of the criteria for neurobrucellosis (Figure 1).

There is no consensus for choice of antibiotic, dose, and duration of the treatment for neurobrucellosis [1, 29]. Dual- or triple-combination therapy with doxycycline, rifampicin, trimethoprim-sulfamethoxazole, streptomycin, or ceftriaxone for >2 months was recommended [1, 5, 20, 30]. The sensitivity of *Brucella* species to third-generation cephalosporins is variable. In one study from Turkey, resistance to ceftriaxone was not detected in *Brucella* species [31]. Antimicrobial treatment was continued for 4–9 months in some studies [7, 13, 14, 20, 32]. Our patients were treated for a total of 6 months. Ceftriaxone-based regimens were reported to be more successful with a shorter duration of therapy than the oral standard treatment protocol [33]. However, because our study was observational, rather than a randomized trial, we cannot suggest using ceftriaxone as an alternative agent in neurobrucellosis.

Mortality rates have been reported between 0%–27% in neurobrucellosis cases [5, 7, 20]; sequelae were reported among survivors despite appropriate antibiotic therapy [5, 7, 13, 20, 32]. In our study, 1 patient with neurobrucellosis died of cardiac and cerebrovascular illness and 3 patients with cranial nerve involvements recovered with sequelae.

Our study was restricted with inclusion of hospitalized patients. Diagnosis of neurobrucellosis is more likely among severely ill and hospitalized brucellosis patients, and this may explain our high rate of neurobrucellosis (37.5%). The study was performed with data collected between 2002 and 2005. Unchanged diagnostic and therapeutic approaches in brucellosis make our results still valid and significant for clinical practice.

CONCLUSIONS

Patients with neurologic signs including severe and persistent headache should be considered for potential neurobrucellosis in endemic regions. These patients may need a longer duration of treatment than 6 weeks of standard therapy. *Brucella* bacteria could be isolated from CSF, although the CSF agglutination was negative. *Brucella* TA with Coombs test in CSF is highly sensitive and specific by using a cutoff ≥1:8. MRI and CT might support the diagnosis of neurobrucellosis.

Note

Potential conflicts of interest. All authors: No reported conflicts.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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