

## Original Article

## Clinical and Laboratory Findings in Neurobrucellosis: Review of 31 Cases

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**Background:** Neurobrucellosis is an uncommon complication of brucellosis. The clinical features of neurobrucellosis vary greatly and, in general, tend to be chronic. Many of the laboratory procedures usually employed in the diagnosis of brucellosis frequently give negative results. For these reasons, and because brucellosis is a disease, which is both treatable and curable, the degree of suspicion must be high, especially in endemic areas, so that an early diagnosis can be made to allow suitable treatment to be established.

**Methods:** A retrospective analysis of 31 cases of neurobrucellosis was carried out.

**Results:** Meningitis and meningoencephalitis were the most common form of neurobrucellosis in our patients. The most commonly-used antibiotics were combinations of rifampin, doxycycline, and trimethoprim-sulfamethoxazole.

**Conclusion:** The differential diagnosis of neurobrucellosis is wide. However, the disease should be ruled out in all patients who develop unexplained neurological symptoms, especially in those who live in endemic areas.

*Archives of Iranian Medicine, Volume 11, Number 1, 2008: 21 – 25.*

**Keywords:** Brucellosis • encephalitis • meningitis • neurobrucellosis

### Introduction

Brucellosis, caused by intracellular Gram-negative bacteria of the genus *Brucella*,<sup>1</sup> is a zoonosis. Almost all infections derive directly or indirectly from animal exposure. Transmission to humans occurs after occupational exposure or through ingestion of contaminated food products.

The disease is endemic in Iran and countries bordering the Mediterranean Sea and also occurs in many other countries.<sup>2</sup> It is a multisystem infection that can involve almost any organ system and may present with a broad spectrum of clinical presentations. Symptoms of brucellosis are variable in nature, and none are specific enough to make the diagnosis. Nervous system involvement

may be the only manifestation of “focal” chronic brucellosis. The nervous system may be one of several systems involved in chronic “diffuse” brucellosis.

The occurrence of neurobrucellosis during the acute phase of illness may be due to direct deleterious effects of organisms invading nervous tissues, to the release of circulating endotoxins, or to the immunologic and inflammatory reactions of the host to the presence of these organisms within the nervous system or within other tissues of the body.

Neurologic involvement of the central nervous system (CNS) has been detected in 3–5% of the patients with brucellosis.<sup>3</sup>

Signs and symptoms referable to CNS involvement typically include headache with or without meningeal irritation and can occur early in the course of the disease or as late as one year after the onset of systemic symptoms.<sup>3–6</sup>

Neurobrucellosis can result in a multitude of nervous system manifestations. The most common presentation is as a typical meningitis or meningo-

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Accepted for publication: 9 May 2007

encephalitis, which is acute and can occur either as the only sign of infection or in the context of a systemic disease.<sup>3, 6, 7</sup>

Patients with acute infection can have cranial nerve palsies that usually resolve completely with administration of antibiotics, whereas those with chronic CNS infection often have permanent neurologic deficits. Various chronic manifestations are perhaps best divided into those presenting with peripheral neuropathy or radiculopathy and those presenting with more diffuse CNS involvement including myelitis with cranial nerve involvement and a syndrome of parenchymatous dysfunction.<sup>3, 6</sup> Symptoms of the peripheral neuropathy and radiculopathy include back pain, areflexia, and paraparesis with involvement of the proximal nerve radicals. In patients with diffuse CNS involvement, myelitis is evidenced by back pain, spastic paraparesis, and demyelination and can also occur with cerebellar dysfunction. The syndrome of parenchymatous dysfunction can occur at any point in the CNS but it most commonly affects the cerebellum, spinal cord, and cerebral white matter. Meningovascular complications, in particular mycotic aneurysms, ischemic strokes, and subarachnoid hemorrhage, are relatively common.<sup>6, 7</sup> Neurobrucellosis can present with other rare neurologic manifestations including isolated intracranial hypertension,<sup>8, 9</sup> Guillain-Barre syndrome,<sup>10</sup> solitary extra-axial posterior fossa abscess,<sup>11</sup> diabetes insipidus,<sup>12</sup> pituitary abscess,<sup>13</sup> cerebral venous thrombosis,<sup>14</sup> and subdural hemorrhage.<sup>15</sup>

Examination of the cerebrospinal fluid (CSF) typically reveals an elevated protein concentration, a depressed glucose concentration, and a moderate leukocytosis composed mainly of lymphocytes.<sup>3, 5, 6</sup> The exception is the cerebellar syndrome, in which the protein concentration is elevated but there is no leukocytosis.<sup>16</sup> Cultures of CNS tissue and fluid are frequently sterile; however, bacteria are occasionally recovered from the CSF and from the brain granuloma.<sup>16</sup> Granulomatous inflammation of the meninges and of the brain parenchyma is also found and can be accompanied by central necrosis.<sup>1</sup>

Imaging abnormalities in neurobrucellosis are variable and may mimic other infectious or inflammatory conditions. The imaging appearance reflects inflammatory or demyelinating processes, or a vascular insult and does not always correlate with the clinical picture. The reasons for such variable manifestations remain obscure.<sup>17</sup>

The mortality rate of neurobrucellosis in the postantibiotic era is 0 – 5.5%, but permanent neurologic deficits, particularly deafness, are common.<sup>5, 6</sup>

The objective of this report was to analyze the clinical presentation of neurobrucellosis with special emphasis on clinical and laboratory features.

## Patients and Methods

In a retrospective study, we found 31 consecutive patients with neurobrucellosis admitted to Department of Infectious Diseases, Imam Khomeini Hospital, Tehran, Iran, between 1990 and 2004.

The diagnosis of neurobrucellosis requires satisfaction of the following criteria: 1) clinical features of the illness compatible with a known neurobrucellosis syndrome; 2) typical CSF changes (pleocytosis, elevated protein concentration); 3) positive results of either blood or bone marrow or CSF culture or appropriate serological tests (e.g., agglutination test titers of >1:160 in blood or any positive titer in CSF); 4) clinical improvement after starting an appropriate treatment; and 5) inability to prove a more suitable alternative diagnosis.

Epidemiologic features, clinical picture, and laboratory findings were collected and analyzed. According to clinical presentation and laboratory findings, the patients were classified into five groups: 1) diffuse encephalopathy/meningoencephalitis; 2) meningitis; 3) peripheral neuritis/radiculitis; 4) brain abscess; and 5) epidural abscess.

## Results

During the past 15 years, we had 31 patients with neurobrucellosis. Nineteen (61%) patients were males and the remaining (39%) were females. The mean age of the patients was 35 (range: 13 – 72) years. The past usage of unpasteurized dairy products was negative in only five (16%) patients. Five (16%) patients had past history of brucellosis from one to 11 months before admission; four of these five patients had been treated with antibrucella agents for one to four months. Twenty patients had been on different medications, 12 (39%) of whom had used drugs, which had some effects on brucellosis too.

Table 1 summarizes the presenting pictures of neurobrucellosis in our patients.

**Table 1.** Presentations of neurobrucellosis in the patients.

Diagnosis	Frequency
Meningoencephalitis	14
Meningitis	12
Polyradiculopathy	3
Brain abscess	1
Epidural abscess	1
<b>Total</b>	<b>31</b>

The period between the first symptom and diagnosis ranged from five days to six months. Among 26 patients who were admitted with the diagnosis of meningoencephalitis or meningitis, the duration of illness in two with meningitis was less than one week; in two patients, it was between one week and three months; and in 20, it was more than three months. Two patients had recurrent meningitis.

Headache was the most common symptom (n=17; 55%). Other symptoms included fever and chills in 15 (49%) patients, vomiting and exhaustion, each in nine (29%), and decreased level of consciousness in eight (26%) patients. Two patients had paraplegia and visual disturbances. Ataxia and seizure were each observed in one case.

Twenty-two (71%) patients had fever. Twenty (65%) had signs of meningeal irritation. Splenomegaly was observed in eight (26%) patients. We observed one patient with spastic paraplegia.

Lumbar puncture was done in all but two patients—one with brain abscess and another with epidural abscess. Pleocytosis with lymphocytes predominancy was observed in all patients (in one patient polymorphonuclear cells were dominant). CSF protein was measured >100 mg/dL in 23 (80%) patients. CSF sugar was <40 mg/dL in 24 (83%) patients. Tube agglutination test (STA) or Wright test was performed on 16 CSF samples; 14 samples were found positive. Results of CSF STA are shown in Table 2. Blood cultures were positive for *Brucella melitensis* in five (16%) patients;

**Table 2.** Results of CSF tube agglutination test (Wright test) in the patients.

Serum agglutination test (STA)	Frequency (%)
Negative	2 (13%)
1/20	3 (19%)
1/40	3 (19%)
1/80	4 (25%)
1/160	2 (13%)
1/320	1 (6%)
1/640	0 (0%)
1/1280	1 (6%)
<b>Total</b>	<b>16</b>

**Table 3.** Results of serum tube agglutination test (Wright test) in the patients.

Serum agglutination test (STA)	Frequency (%)
Negative	2 (7%)
1/80	1 (3%)
1/160	10 (32%)
1/320	5 (16%)
1/640	3 (10%)
1/1280	6 (19%)
1/2560	4 (13%)
<b>Total</b>	<b>31</b>

cultures became positive after a median duration of 5.5 days. CSF culture, taken for 17 patients, was found positive in four (13%). Bone marrow culture was positive in three (10%) patients.

Results of STA are shown in Table 3. In two patients with negative serum Wright test, CSF culture was found positive.

Thirteen patients had brain computed tomography (CT) or magnetic resonance imaging (MRI), which showed hydrocephalia in two patients, brain abscess in one, and epidural abscess in one (the one who had spastic paraplegia). This patient had abscess drainage with positive culture for *Brucella*.

All patients received antibiotic therapy with rifampin, doxycycline and ceftriaxone, or gentamin, initially, which then were continued with rifampin, doxycycline with or without cotrimoxazole for four to 12 months. Four patient received corticosteroids. In the follow-up, one patient died two weeks after beginning of the treatment because of unknown reason; others recovered uneventfully. Relapse was not observed in six to 12 months of follow-up.

## Discussion

Brucellosis is a zoonosis throughout the world. It has a particularly high incidence rate in Iran, especially in rural areas, largely due to the consumption of unpasteurized milk and cheese.

Human brucellosis is diagnosed on the basis of epidemiologic and clinical findings and bacteriologic and serologic tests.

Symptoms of the disease may mimic many diseases and show varied manifestations of acute and chronic infection. Complications of brucellosis sometimes may lead to misdiagnosis.

Neurobrucellosis is an uncommon complication of brucellosis (<5%) and can present as meningitis, encephalitis, myelitis-radiculoneuritis, brain abscess, epidural abscess, meningovascular

complications, peripheral neuropathy, and psychosis.<sup>18</sup> In a retrospective study on 505 patients with brucellosis from 1990 through 1999 in Tehran, 21 (4.15%) patients had neuronbrucellosis.<sup>19</sup>

A depressed immune status is believed to be a risk factor for developing neurobrucellosis. There is a case report of neurobrucellosis in a 13-year-old recipient of a cadaveric renal transplantation.<sup>20</sup>

Sometimes, neurologic findings may be the only signs of brucellosis.<sup>6,7,21</sup> The most common presentation of neurobrucellosis is acute meningitis.<sup>22</sup> Acute *Brucella* meningitis is usually characterized by sudden onset of fever, headache, and nuchal rigidity. Psychiatric and motor-sensory disorders are also common. However, since similar symptoms may be present in some patients who have systemic brucellosis without neurologic involvement and in those who have infectious meningitis due to other microorganisms, the diagnosis of neurobrucellosis requires direct or indirect evidence of *Brucella* in the CSF. In our patients, meningoencephalitis and meningitis were the most common presentations of neurobrucellosis. Three patients had polyradiculopathy; one patient presented with spinal epidural abscess and another had brain abscess. Of 13 patients with neurobrucellosis from Ankara, Turkey, 10 had chronic and three had acute meningitis. Two patients had only psychiatric disorders. Cranial nerve involvement was observed in three patients.<sup>23</sup> In a report on 12 cases from Bikaner (North-West of India), 12 of 92 patients with brucellosis revealed evidence of neurobrucellosis of whom four had meningoencephalitis, two had myelitis leading to spastic paraparesis, five had polyradiculoneuropathy, and one had polyneuro-radiculomyeloencephalopathy.<sup>24</sup>

Blood culture is not an ideal test for diagnosis of neurobrucellosis because of low yield and long time it requires.<sup>24</sup> Because of the low rate of *Brucella* isolation from CSF (<20%), the diagnosis of neurobrucellosis usually depends on the detection of specific antibodies in CSF.<sup>3,25</sup>

Antibodies were detected in the CSF samples from patients with proven neurobrucellosis but not in the CSF samples from patients who had systemic brucellosis without neurologic involvement.<sup>25</sup>

In our study, all patients with meningitis had pleocytosis in CSF. In all cases but one, mononuclear cells were dominant. CSF protein in the majority of these patients was elevated and CSF

glucose was <40 mg/dL.

Result of agglutination test for *Brucella* in serum was <1/160 in three patients in whom the diagnosis of neurobrucellosis was made based on a positive CSF agglutination test in one and positive CSF culture in two patients.

The diagnosis of human neurobrucellosis usually relies on the detection of antibodies to *Brucella* lipopolysaccharide (LPS) in CSF by agglutination tests or enzyme-linked immunosorbent assay (ELISA). Baldi et al described detection of immunoglobulin G (IgG) against cytoplasmic proteins (CP) of *Brucella* spp by ELISA and Western blotting in seven CSF samples from five patients with neurobrucellosis and suggested that in addition to its usefulness in the serologic diagnosis of human systemic brucellosis, the ELISA with CP antigen can be specifically used for the diagnosis of human neurobrucellosis.<sup>25</sup> In 13 patients with neurobrucellosis from Ankara, Turkey, 12 had positive agglutination titers in CSF; only three had positive blood cultures and three others had positive CSF cultures.<sup>23</sup>

In our study, 14 of 16 patients has positive agglutination test in CSF. Five had positive blood culture, three had positive bone marrow culture, and four patients had positive CSF culture. In one patient, neurobrucellosis was diagnosed despite negative CSF culture and serology, just based on the clinical response and disappearance of CSF abnormality with anti-*Brucella* treatment.

In two patients, CSF Coombs Wright test was done that was slightly higher than CSF Wright test. Since CSF Wright test may be negative, it is better to use CSF Coombs Wright test, in addition to CSF Wright test and culture, in patients with suspicious neurobrucellosis.

Neurobrucellosis presenting as a focal brain mass has rarely been demonstrated on imaging studies.<sup>26</sup> In our patients, brain abscess and epidural abscess were detected in brain CT and spine MRI of two patients.

Treatment of neurobrucellosis included concurrent administration of three of the following drugs: doxycycline, rifampin, streptomycin, cotrimoxazole, ceftriaxone, or ciprofloxacin.<sup>27</sup> Antimicrobial treatment in our patients began with concurrent administration of three antibiotics for a minimum of four months.

The authors point out the importance of specific microbiologic examinations of patients with symptoms that are compatible with neurobrucellosis. In our patients, there were two patients with

chronic meningitis and negative CSF serologic test for *Brucella*, but positive CSF culture.

In summary, physicians in endemic regions must recognize that brucellosis is an infection, which may involve almost any organ system and which may vary markedly in its clinical presentation. In patients living in endemic regions, considering neurobrucellosis in differential diagnosis of any neurologic symptoms, may lead to early diagnosis and treatment, and may decrease the complications.

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