

## Original Article

# Epidemiological, Clinical, and Laboratory Features of Brucellar Meningitis

Hossein Hatami MD MPH<sup>1</sup>, Maryam Hatami MD<sup>2</sup>, Hamid Soori PhD<sup>3</sup>, Ali-Reza Janbakhsh MD MPH<sup>4</sup>, Feizollah Mansouri MD MPH<sup>4</sup>

## Abstract

**Background:** One of the rare complications of brucellosis is mononuclear meningitis, which usually imitates systemic disease.

**Methods:** Documents of patients with confirmed brucellar meningitis hospitalized in Sina Hospital (Western Iran) between 1988 – 2005 were collected.

**Results:** The average age was 26.9. 64% were female and 36% were male. There were 25% confirmed cases in the spring, 21% in summer, 33% in autumn and 21% in winter.

Patient complaints in order of frequency were: headache (95%), vomiting (77%), fatigue (39%), myalgia (15%), movement disorders (15%), arthralgia (13%), sleepiness (13%), and aphasia (3%). The main clinical findings were: nuchal rigidity (74%), splenomegaly (49%), fever (41%), Kernig's (41%), and Brudzinski's signs (39%).

Lukopenia ( $WBC < 4.5 \times 10^9/L$ ; 18%), leukocytosis ( $WBC > 9.5 \times 10^9/L$ ; 20%), and anemia (hemoglobin level  $< 13$  g/dL in men and 12 g/dL in women) were detected in 16% of patients. The Wright agglutination test, with a titer of 1:80 to 1:1280 was present in the serum of all patients, CSF Wright test or Coombs test was positive in half of the patients. Blood, bone marrow and CSF cultures were positive in 6 out of 10 patients.

**Discussion:** The epidemiological aspects of brucellar meningitis are similar to systemic brucellosis and, in most studies; there is no significant difference between them. The sex distribution of patients was different from most studies. Seasonal distribution of the disease did not follow seasonal distribution of systemic brucellosis, however, clinical findings or laboratory changes were similar to Turkey and other studies in Iran. A definite response, without complications and next recurrence, in this study, was achieved with co-trimoxazole plus rifampin for 45 days of therapy.

**Keywords:** brucellosis, meningitis, meningoencephalitis, nurobrucellosis

## Introduction

According to the World Health Organization (WHO), brucellosis is one of the most common zoonotic diseases worldwide and is considered a

reemerging infectious disease in many areas of the world.<sup>1</sup> It causes disability in man, and decreases production of milk, meat, and wool in animals. Brucellosis is considered to be one of the relatively common diseases imported by travelers.<sup>2</sup> According to WHO reports, in 2003 brucellosis has been more prevalent in Syria (23,297 cases), Iran (17,765 cases), and Turkey (14,435 cases).<sup>3</sup> However, the total number of cases reported to the WHO did not exceed 500,000 annually,<sup>4</sup> which is not realistic and are only 4% of the total cases. Although syphilis has been named as the “great imitator” due to the variability in its clinical appearance, however, in countries with a high incidence of brucellosis, the latter shall be named the great imitator due to its imitation of the signs and

**Authors' affiliations:** <sup>1</sup>Department of Public Health, School of Health, Shahid Beheshti University of Medical Sciences, Tehran, <sup>2</sup> Department of Obstetrics and Gynecology, Shohada Tajrish Hospital, Tehran, <sup>3</sup>Department of Epidemiology, School of Health, Shahid Beheshti University of Medical Sciences, Tehran, <sup>4</sup>Department of Infectious Diseases, Kermanshah University of Medical Sciences, Kermanshah, Iran.

**Corresponding author and reprints:** Hossein Hatami MD MPH, School of Health, Shahid Beheshti University of Medical Sciences, Daneshjoo Blvd., Tabnak St., Evin, Tehran, Iran. Tel: +98-212-243-2036, Fax: +98-212-243-2036

E-mail: hatami@hbi.ir

Accepted for publication: 16 June 2010

symptoms of many infectious and non-infectious diseases, and various complications.<sup>5</sup>

Neurological syndromes in brucellosis include meningitis, encephalitis, myelitis, radiculoneuritis, brain abscess, epidural abscess, granuloma, and demyelinating and meningovascular syndromes. Acute or chronic meningitis are the most frequent nervous system complications.<sup>6</sup> Brucellosis meningitis is quite similar to other mononuclear meningitis types, both clinically and laboratory based, while with respect to the epidemiological characteristics it complies with systemic brucellosis.<sup>2</sup> The most malignant mononuclear meningitis is the tuberculous one and the most prevalent are viral types, however, the most curable includes brucellar mononuclear meningitis.<sup>7</sup>

Its incidence is not equal in different studies and comprises of 5 – 7% of the total cases of brucellosis patients admitted to hospitals.<sup>2,8</sup>

Although neurobrucellosis has been reported from Kermanshah (western Iran),<sup>2</sup> Azerbaijan (northwest Iran),<sup>9</sup> Hamadan (western Iran),<sup>10</sup> and Tehran (Imam Khomeini Hospital),<sup>11</sup> but the highest number is being reported here (current study).

This syndrome may be due to the direct effect of the organism on the nervous system. Additionally, chronic forms of the disease may be attributed to the continuance of the microorganism's intracellular effects or start up of the immune mechanisms, which result in myelin destruction.<sup>12</sup>

Peripheral nerve involvement, direct involvement of the spinal cord and primary involvement of sciatica are considered to be rare complications. The meningitis type, which results in medulla involvement and is secondary to spondylitis is also the result of epidural inflammation. The sensory disorder usually includes paresthesia and sometimes cognitive disorders, and often results from spinal cord compression and inflammation.<sup>13</sup>

The objectives of this report were to analyze the clinical presentations and laboratory changes of brucellar meningitis with special emphasis on response to therapy and prognosis.

## Patients and Methods

A cross-sectional analysis of data collected with the use of a checklist tool and information gathered from the files of patients who were admitted to the Department of Infectious Diseases, Sina Hospital, Kerman-

shah between 1988 and 2005 was undertaken. The case definition for selection of valid files was based on clinical, serological, and microbiological criteria. Patients were selected who were suffering from mononuclear meningitis and had positive agglutination tests (Wright or Coombs Wright, with a titer of more than or equal to 1:80) of serum and/or cerebrospinal fluid (CSF) samples, and positive blood, bone marrow or CSF cultures. The selected files were approved by the university academic infectious diseases specialists.

The definitions of leucopenia, leukocytosis, normal leukocyte count, anemia, and ESR are based on reference values.<sup>14</sup>

## Results

During the aforementioned time, 793 patients were admitted with clinical presentation of brucellosis, of which 39 (5%) suffered from brucellar meningitis. The mean age of the patients was 26.9 (SD=2.4), with a range of 5 to 71, respectively (Figure 1). Sixty-four percent were females, 36% males, and a total of 25% were admitted in the spring, 21% in summer, 33% in autumn, and 21% in winter. Nearly all had consumed unpasteurized dairy products.

The most common symptoms were: headache (95%), nausea and/or vomiting (77%); however, other complaints were: weakness (39%), myalgia (15%), cough (15%), motor disorders (15%), arthralgia (13%), drowsiness (13%), and aphasia (5%). The major clinical findings included: neck-stiffness (74%), splenomegaly (49%), fever (41%), Kernig's sign (41%), and Brudzinsky's sign (39%) (Figure 2).

Laboratory findings included: leucopenia 20%, leukocytosis 18%, and normal leukocyte count in 62% of them. Relative lymphocytosis was found in 50% of patients and anemia in 16%. Although the sedimentation rate in 71% of cases was within the normal range, it was elevated in 21% of cases. The Wright agglutination test with titers of 1:80 to 1:1280 were seen in all patients' serums (Table 1); in half of the cases, the CSF Wright test or Coombs test was positive (Wright or Coombs-Wright CSF tests were positive in a titer of 1:80 in six patients; 1:160 in one patient; 1:640 in four patients and 1:1280 in two patients). Additionally, blood, bone marrow, and CSF cultures were positive in six out of ten patients were positive (blood and bone marrow in two patients; blood and CSF in three

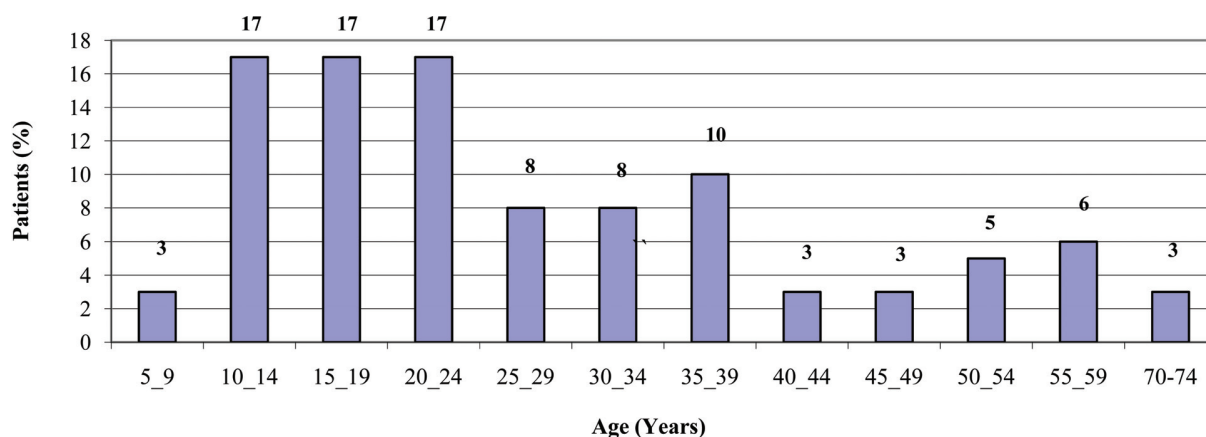


Figure 1. Age distribution of patients with brucellar meningitis

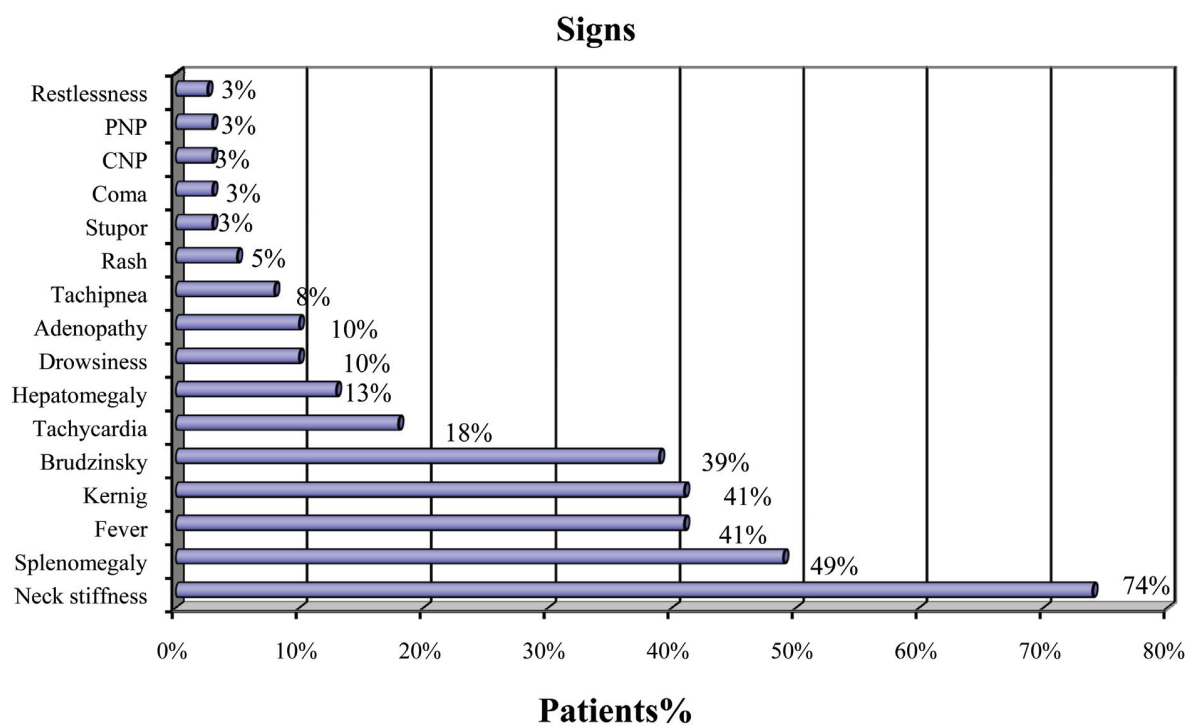


Figure 2. Distribution of patients with brucellar meningitis according to their signs at the time of admission

Table 1. Distribution of patients suffering from brucellar meningitis based on Wright test criterion

Wright agglutination test titer	Patients	
	Number	Percentage
1:80	1	2.6
1:160	4	10.3
1:320	13	33.3
1:640	11	28.2
1:1280	10	25.7

**Table 2.** Characteristics of the CSF in patients suffering from brucellar meningitis

Status of cerebrospinal fluid WBC (cells/mm <sup>3</sup> )	Patients (%)
0 – 9	3
10 – 99	12
100 – 499	54
500 – 999	21
1000+	10
Lymphocytes (%)	Patients (%)
0 – 24	18
25 – 49	5
50 – 74	18
75 – 100	59
Status of cerebrospinal fluid protein (mg/dL)	Patients (%)
6 – 45	43
46 – 280	57

patients and bone-marrow in one patient).

The results of CSF analysis can be seen in Table 2. *Brucella melitensis* was isolated from six out of ten cultured specimens (three specimens from blood and CSF, one from blood, and two only from bone marrow aspirate).

All patients were treated with usual doses of oral co-trimoxazole plus rifampin for a six-week period. Complete recovery was seen in all patients, without any complications, except for three cases which resulted in nausea and vomiting. Those cases were prescribed intra-venous co-trimoxazole instead of oral. Over several year follow-up period neither treatment failure nor relapse were seen.

## Discussion

As brucellar meningitis is considered as one of the clinical presentations of systemic brucellosis, the respective epidemiological features including age, gender, and seasonal distributions are similar to the systemic disease and in most studies, no significant difference is noted.<sup>15</sup> Although, amongst a study in Turkey in 2006 on 20 cases of brucellar meningitis, 60% of the patients were males and 40% females<sup>16</sup> and in three studies in Tabriz (70% male and 30% female),<sup>9</sup> Hamadan (60% male and 40% female),<sup>10</sup> and Tehran (61% male and 39% female).<sup>11</sup> The percentages of males were greater than females. In our study, however, 64% of the patients were female and 36% were male for which there was no definite explanation. This does not correlate with seasonal frequency in our total of 793 cases mentioned above and the admitted cases during autumn were more than other

seasons. Unexpectedly, the highest number of cases did not occur during spring and summer. With the exception of autumn, the other three seasons had similar numbers, which may be a result of the slow trend and gradual formation of the brucellar meningitis and its sub acute nature in most cases. Perhaps the admitted cases during autumn and winter were the cases which were initiated in spring and summer.

In one study headache and meningeal signs were found in 42% of the patients with neurobrucellosis,<sup>13</sup> and in 33% for another study<sup>14</sup>; however, 95% of our patients presented with these signs, which was more than other reports from Iran (Tabriz 70%, Hamadan 75%, and Tehran 55%).<sup>9–11</sup> According to the frequency of splenomegaly, our study was similar to a study in Kuwait.<sup>17</sup>

None of the other CNS complications of neurobrucellosis such as: arachnoiditis, cerebellar syndrome, hemi-parkinsonism, chorea, anterior myelitis, Guillan-Barre syndrome, and encephalitis<sup>13</sup> appeared in our patients, with the exception of sub-arachnoid hemorrhage, which occurred in the first patient (13-year-old girl), which was attributed to the rupture of a mycotic aneurysm, one of the well known complications of brucellar meningitis<sup>18</sup> and was cured by drug therapy.

With the use of castaneda culture media, *Brucella melitensis* was isolated from either the peripheral blood, bone marrow or cerebro-spinal fluid of six out of ten cases. It should be mentioned that finding *Brucella* in CSF is not common; however, most of the brucellar meningitis cases have been reported from the Mediterranean region where *Brucella melitensis* is the most common type.<sup>13</sup>

Some authors considered the combination of tetracycline or doxycycline in addition to rifampin as drug therapy. Others have proposed the third generation of cephalosporines. However, due to the decisive effect of co-trimoxazole in addition to rifampine in Kermanshah and Tabriz,<sup>9</sup> and lack of failure of the therapies and potential complications; it seems, the regimen of choice should include these two drugs. Additionally the duration of therapy hardly exceeded two months, according to these studies.<sup>2</sup> WHO experts also advise this regimen for the treatment of neurobrucellosis.<sup>8</sup> While the duration of therapy in 19 cases in Kuwait was more than eight weeks; it should be noted that all patients with meningo-encephalitis responded to therapy in 1 – 2 weeks, and permanent neurological sequelae did not appear. However, those suffering from peripheral nerve involvement responded slowly to the therapy and a slight weakness remained in their affected body parts. Finally those who suffered from diffuse CNS involvement had a worse prognosis.<sup>13</sup> In another study, optic nerve atrophy and cranial nerve deficits continued after therapy.<sup>19</sup> In a study in Spain, anti-microbial agents were continued until glucose normalized in the CSF. The leukocytes were reduced to less than 100 cells/mm<sup>3</sup> and antibody titers reduced. The average duration of therapy in seven patients with neurobrucellosis was reported as 8.5 months, of which two of them suffered from disease relapse.<sup>13</sup> However, in our cases none of these problems appeared and with the same regimen (co-trimoxazole and rifampine) a complete recovery resulted with the exception of three cases which resulted in nausea and vomiting. In those cases, we prescribed intra-venous co-trimoxazole. These two drugs were successfully used orally until therapy completion. During the follow-up period of several years, neither treatment failure nor relapse was seen.

In the differential diagnosis of brucellar meningitis, all of the infectious and non-infectious mononuclear meningitis are considered. However, in our country the most common are viral meningitis and the most important is tuberculous meningitis. Thus, at the time of clinical examination of patients with suspected brucellar meningitis, both tuberculous and viral meningitis should also be considered and the appropriate tests done in order to confirm or rule them out.

We must pay more attention to the patient's age, duration of disease, and existence or non-existence of fever and splenomegaly while considering relative

lymphocytosis in peripheral blood, glucose levels, and protein changes in CSF and serological brucellar diagnostic tests. Most viral meningitis occur during the childhood and adolescent periods and rapidly progresses, thus the patient seeks timely medical care. Whereas the progression of tuberculous and brucellar meningitis are slower, may occur at any age and the probability of an elevated lymphocyte count and protein, and potential decrease of glucose in tuberculous and brucellar meningitis are more than viral meningitis. Thus, serological tests for brucellosis, in most cases, helps in identification and differentiation between these three diseases.<sup>2,7</sup>

After all, many findings of this study, including the decisive therapy response and lack of relapse are quite similar to the Kuwaiti studies,<sup>20</sup> which may be due to the similarity of the etiologic agent, early diagnosis and onset of therapy.

## References

1. Russo G, Pasquali P, Nenova R, Alexandrov T, Ralchev S, Vullo V, et al. Reemergence of human and animal brucellosis, Bulgaria. *Emerg Infect Dis*. 2009; **15**: 314 – 316.
2. Hatami H, Saghari H. Epidemiology of brucellosis. In: Hatami H, ed. *Epidemiology and Control of Diseases Related to Bioterrorism*. 2<sup>nd</sup> ed. Tehran, Seda Publishing Co; 2003: 195 – 260.
3. Pappas G, Akritidis N, Bosilkovski M, Tsianos E. Brucellosis. *N Engl J Med*. 2005; **352**: 2325 – 2336.
4. Pappas G, Papadimitriou P, Akritidis N, Christou L, Tsianos EV. The new global map of human brucellosis. *Lancet Infect Dis*. 2006; **6**: 91 – 99.
5. Hatami H. Epidemiology of brucellosis. In: Hatami H, Razavi SM, Eftekhari AH, eds. *Textbook of Public Health*. 2<sup>nd</sup> ed. Tehran: Arjman Publishers; 2006: 1206 – 213.
6. Young EJ. Brucella species. In: Mandell D. *Bennett's Principles and Practice of Infectious Diseases*. 7<sup>th</sup> ed. United States: Churchill Livingstone; 2010: 2921 – 2926.
7. Hatami H. Comparison of TB meningitis, neuro-brucellosis and viral meningitis in patients admitted in Sina Hospital Kermanshah. An oral presentation in the Congress of Tuberculosis, Rasht (northern Iran). 1995: 312 – 329. Available from: URL: [http://www.elib.hbi.ir/persian/PERSIAN\\_COMPUTERIZED\\_BOOKS\\_FOR\\_DOS/congereh.zip](http://www.elib.hbi.ir/persian/PERSIAN_COMPUTERIZED_BOOKS_FOR_DOS/congereh.zip) (Cited 2010/09/25)
8. Food and Agriculture Organization of the United Nations, World Organization for Animal Health,



- and World Health Organization. Brucellosis in human and animals. Geneva: World Health Organization; 2006. WHO/CDS/EPR/2006.7 Available from: URL: <http://www.who.int/entity/csr/resources/publications/Brucellosis.pdf> (Cited 2010/09/25)
9. Pourhassan A. Clinical and laboratory findings in neurobrucellosis. *Iran J Clin Infect Dis*. 2007; **2**: 71 – 76.
10. Ranjbar M, Rezaiee AA, Hashemi SH, Mehdipour S. Neurobrucellosis: report of a rare disease in 20 Iranian patients referred to a tertiary hospital. *East Mediterr Health J*. 2009; **15**: 143 – 148.
11. Haji-Abdolbagi M, Rasooli-Nejad M, Jafari S, Hasihi M, Soudbakhsh A. Clinical and laboratory findings in neurobrucellosis: review of 31 cases. *Arch Iran Med*. 2008; **11**: 21 – 25.
12. Shakir RA. Clinical category of neurobrucellosis: a report of 19 cases. *Brain*. 1987; **110**: 213 – 223.
13. Bouza E, Garcia dela Torre M, Parras F, Guerrero A, Rogrguez-Cr  ixems M, Gobernado J. Brucellar meningitis. *Rev Infect Dis*. 1987; **9**: 810 – 822.
14. Kratz A, Persce MA, Fink DJ. Laboratory values of clinical importance. In: Fauci AS, Braunwld E, Kasper DL, eds. *Harrison's Principles of Internal Medicine*. 17<sup>th</sup> ed. New York: McGraw Hill; 2008: 2755 – 2756.
15. Kokoglu OF, Hosoglu S, Geyik MF, Ayaz C, Akalin S, Buyukbese MA, et al. Clinical and laboratory features of brucellosis in two university hospitals in Southeast Turkey. *Trop Doct*. 2006; **36**: 49 – 51.
16. Yetkin MA, Bulut C, Erdinc FS, Oral B, Tulek N. Evaluation of the clinical presentations in neurobrucellosis. *Int J Infect Dis*. 2006; **10**: 446 – 452.
17. Lulu AR, Araj GF, Khateeb MI, Mustafa MY, Yusuf AR, Fenech FF. Human brucellosis in Kuwait: a prospective study of 400 cases. *Q J Med*. 1988; **66**: 39 – 54.
18. Mousa AR, Muhtaseb SA, Almudallal DS, Khodeir SM, Marafie AA. Osteoarticular complications of brucellosis: a study of 169 cases. *Rev Infect Dis*. 1987; **9**: 531 – 543.
19. Adaletli I, Albayram S, Gurses B, Ozer H, Yilmaz MH, Gulsen F. Vasculopathic changes in the cerebral arterial system with neurobrucellosis. *AJNR Am J Neuroradiol*. 2006; **27**: 384 – 386.
20. Lubani MM, Dudin KI, Araj GF, Manandhar DS, Rashid FY. Neurobrucellosis in children. *Pediatr Infect Dis J*. 1989; **8**: 79 – 82.