Original Article

Human brucellosis in Turkey: different clinical presentations

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Abstract

Introduction: Brucellosis is still endemic in Turkey and presents a major public health risk. The aim of this study wasto investigate the clinical and laboratory properties and complications of brucellosis cases.

Methodology: The files of 370 patients (162 males, 208 females) with brucellosis between March 2006 and January 2012 were analyzed retrospectively.

Results: The mean age of patients was 39, 6±18.2 years. The major risk factor was unpasteurized dairy products in 155 (41.8%) cases. The complications included hematological (58.1%), osteoarticular (48.3%), hepatobiliary (26.7%), gastrointestinal (10%), and genitourinary system involvement (4.8%). The most frequently seen symptoms were weakness (64.3%), fever (63.2%), sweating (62.7%), arthralgia (59.1%), and lack of appetite (47.8%). A total of 261 patients (70.5%) were acute, 73 patients (19.7%) were subacute, and 36 patients (9.7%) were chronic. In the laboratory tests, AST, ALT and CRP levels were found as elevated in 27.6%, 21.6%, and 69.6% of the patients, respectively. On complete blood count analysis, leukopenia (21.4%), thrombocytopenia (23%), and anemia (70%) were determined. Pancytopenia was more common in acute cases ($p = 0.019$). Osteoarticular complications increased significantly with increased age ($p = 0.005$).

Conclusions: Brucellosis is a common disease that may be accompanied by serious complications. In endemic regions of brucellosis, people should be taught to avoid unpasteurized dairy products. Clinicians must be aware of multiple system involvement in brucellosis, especially hematological and musculoskeletal systems. Hematological abnormalities occurring during the course of the disease may be misdiagnosed as hematological malignancies.

Key words: brucellosis; complications; southeastern of Turkey

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Introduction

Brucellosis is one of the most widespread zoonoses worldwide [1]. It is a zoonotic infection transmitted to humans by contact with fluids from infected animals (sheep, cattle, goats, pigs, or other animals) or derived food products such as unpasteurized milk and cheese [1-3]. Brucellosis has high morbidity both for humans and animals; it is an important cause of economic loss and a public health problems in many developing countries [2].

Brucellosis is a systemic disease that can involve any organ or system of the body. The clinical presentation can vary from asymptomatic infection with seroconversion to a full-blown clinical picture of fever, night sweats, and joint manifestations; rarely, there is hepatic, cardiac, ocular, or central nervous system involvement [4]. Complications can be very diverse depending on the specific site of infection. Osteoarticular, genitourinary, gastrointestinal, nervous, cardiovascular, skin and mucous membranes, and respiratory complications have been observed [4]. Osteoarticularinvolvement is the most frequent complication of brucellosis [1,5,6].

The diagnosis of brucellosis requires the isolation of Brucella from blood or body tissues or the combination of suggestive clinical presentation and positive serology [1,7]. The Rose Bengal test (RBT), complement fixation test (CFT), standard agglutination test (SAT), competitive enzyme-linked immunosorbent assay (cELISA), fluorescence polarization assay (FPA), as well as real-time PCR are used for diagnosis [1,7].

The aim of this study wasto investigate the clinical properties of Brucella cases and to determine if there is a correlation between the complications and various factors, such as age, clinical type, and laboratory results derived from ourhospital databases.

Methodology

In this study, the registries of two big hospitals in Kahramanmaras city (located in the southeastern part of Turkey) were used; these included Kahramanmaras State Hospital and Research Hospital of Kahramanmaras Sutcu Imam University. The files of the patients applying to these hospitals between March 2006 and January 2012 were analyzed retrospectively. The diagnosis of brucellosis was established by clinical signs and symptoms in the presence of a positive Brucella STA test (titer: 1/160) or a minimum four fold increase in serum antibody titer between two serum samples taken two to three weeks apart and/or growth of *Brucella* spp. in blood or sterile body fluid cultures. In the Wright agglutination test, the serum dilution wa sconducted between 1:20 and 1:2560. Blood culture samples were treated for 14 days in a BACTEC 9240 system.

The patients were allocated into three different groups according to their age and clinical types. The first group included patients under 15 years of age; the second group included patients between 15 and 45 years of age; and the third group included patients older than 45 years of age. The cases was divided into three groups according to the duration of presenting symptoms: acute, subacute, and chronic. Cases with symptoms lasting fewer than 8 weeks were grouped as acute; cases with symptoms lasting between 8 and 52 weeks were classified as subacute; and cases with symptoms lasting more than 52 weeks were classified as chronic. Age, sex, symptoms, family history (presence of family member experiencing brucellosis previously), potential route of infection, laboratory parameters (white blood cell [WBC] count) and C-reactive protein (CRP) complications, diagnostic methods (serology/culture), clinical type (acute, subacute, chronic), and treatment data of 370 patients totally were recorded by investigators on the data form.

Complications related to the patients' groups and clinics were compared. Complications of the disease were determined and groupedaccording to the organ or system involved as defined below.

Osteoarticular involvement included inflammatory signs (heat, redness, pain, swelling, or functional disability) in any peripheral joint or unrelieved pain at rest along with radiological alterations and/or radionuclide uptake in any deep joint, evaluated independently by both the clinician and the radiologist [2].

Central nervous system involvement was defined as the presence of meningitis, encephalitis, myelitis-radiculoneuronitis, brain abscess, epidural abscess, granuloma, demyelinating and meningovascular syndromes, or sensorineural hearing loss. Diagnosis of neurobrucellosis includes lymphocytic pleocytosis, elevated protein, and normal or low glucose concentrations. Gram stains and cultures of cerebrospinal fluid are often negative; therefore, the diagnosis depends on the presence of specific antibodies or real-time polymerase chain reaction [1].

Hematological involvement included laboratory abnormalities such asanemia, leukopenia, thrombocytopenia, and clotting disorders [1]. Anemia, thrombocytopenia, and leukopenia were defined as hemoglobin levels of <12.2 g/dL, platelet count of <142,000/mm^3, and leukocyte count of <3,500/mm^3, respectively.

Hepatic involvement was defined as a more than two fold increase in aminotransferase levels without any other etiological explanation and/or serum total bilirubin levels of 2.5 g/dL. [2]. Gastrointestinal complications were considered if there were any signs or symptoms of involvement such as nausea/vomiting, diarrhea, constipation, or abdominal tenderness [1].

The ethics committee of the Kahramanmaras Sutcu Imam University of Medical Sciences approved the study.

Statistical analyses were performed using SPSS version 15.0 (SPSS, Chicago, USA). Frequency of symptoms and complications according to age and sex and frequency of complications according to clinical type were compared using the Chi-square test. Statistical significance level was accepted as $p < 0.005$.

Results

More than half of 370 patients with brucellosis (56.2%) assessed in the study were female. The age of the patients enrolled in the study ranged from 3 to 82 years with an average age of 39.6±18.2. A total of 50.4% ofpatients were from rural areas and 49.3% were from urban areas. Twenty-two percent of the patients had a positive family history. Potential route of infection was not explained in the registry of many patients (44.5%). The potential route of infection was unpasteurized products in 75.6% of 205 patients with knowledge of the potential route of infection.

In terms ofclinical type, most of the patients (70.5%) hadacute brucellosis. The most frequent symptom reported was weakness (64.3%), followed by fever (63.2%) and arthralgia (59.1%). Clinical features of the patients are given in Table 1.

According to the results of the diagnostic serum agglutination test, serological titer was above 640 in 62.2% of the patients. Liver enzymes were evaluated at the beginning, and AST and ALT levels were found to be elevated in 27.5% and 21.6% of patients, respectively. CRP levels at diagnosis were found to be high in 69.1% of the patients. On complete blood count analysis, leukopenia was found in 21.3% of the patients, thrombocytopenia in 22.9%, anemia in 70%,and pancytopenia in 6.5% of the patients. Laboratory findings of the patients during diagnosis are shown in Table 2.

The percentage of any complication in the patients was 89.7%. Hematological complications were the most common ones, affecting more than half of the patients (58.1%). These complications were followed in frequency by bone (48.3%) and organomegaly (39.4%) complications. Among bone complications, the most common ones were spondylocystitis (29.1%) andsacroileitis (13.7%). Hepatosplenomegaly was seen in 14.3% of the patients, hepatomegaly in 13.5%, and splenomegaly in 11.6%. Hepatobiliary complications developed in 26.8% of the patients. Complications secondary to brucellosis in study patients are shown in Table 3.

Complications in different age groups were compared. Hematological, hepatobiliary, and gastrointestinal complications were seen more frequently in the young age group as compared to the olderage group;however, the difference was not statistically significant. On the other hand, osteoarticular complications increased significantly with age ($p = 0.005$). Complication rates between males and females did not show a statistically significant difference. Similarly, there was no significant difference between clinical types regarding complications. Pancytopenia was found to be more frequent and statistically significant in acute cases (8.8%) as compared to subacute (1.4%) and chronic (0.1%) cases ($p= 0.019$). Complications according to age group are shown in Table 4.

Table 1. Clinical features of the patients (n = 370)

Clinical characteristics	n (%)
Presence of family history	82 (22.1)
Possible route of transmission	
Unknown	165 (44.5)
Unpasteurized dairy products	155 (41.8)
Farmers	33 (8.9)
Unpasteurized dairy products + farmers	17 (4.5)
Clinical type	
Acute	261 (70.5)
Subacute	73 (19.7)
Chronic	36 (9.7)
Symptoms	
Weakness	238 (64.3)
Fever (> 38.3°C)	234 (63.2)
Sweating	232 (62.7)
Arthralgia	219 (59.1)
Lack of appetite	177 (47.8)
Myalgia	149 (40.2)
Back pain	136 (36.7)
Headache	99 (26.7)
Weight loss	93 (25.1)
Diarrhea or constipation	78 (21.0)
Nausea	68 (18.3)
Signs	
Hepatosplenomegaly	53 (14.3)
Hepatomegaly	50 (13.5)
Splenomegaly	43 (11.6)
Lymphadenopathy	10 (2.7)

Table 2. Laboratory findings of the patients during diagnosis

Laboratory signs	n (%)
Agglutination titers	
160↑	24 (6.4)
320↑	115 (31.0)
640↑	229 (61.8)
AST IU/l	
<13	13 (3.5)
13-40	255 (68.9)
>40	102 (27.5)
ALT IU/l	
<7	1 (0.2)
7-45	289 (78.1)
> 45	80 (21.6)
CRP (mg/L)	
Normal	112 (30.2)
High	256 (69.1)
WBC	
< 3500	79 (21.3)
3,500-10,500	257 (69.4)
>10,500	34 (9.1)
Hemoglobin (gram/dl)	
< 12,2	259 (70.0)
12,2-18,1	110 (29.7)
> 18,1	1 (0.2)
Platelets (cell x 10^9/mL)	
< 142,000	85 (22.9)
142,000-424,000	271 (73,2)
> 424,000	14 (3.7)

ALT: aspartate aminotransferase; AST: alanine aminotransferase; CRP: C-reactive protein

Table 3. Complications developed in study patients secondary to brucellosis

	n (%)
Complications (total)	332 (89.7)
Hematological	215 (58.1)
Osteoarticular	
Spondylodiscitis	108 (29.1)
Sacroiliitis	51 (13.7)
Peripheral arthritis	11 (2.9)
Bursitis	4 (1.0)
Synovitis	2 (0.5)
Osteomyelitis	1 (0.2)
Tendinitis	2 (0.5)
Hepatobiliary	99 (26.8)
Gastrointestinal	37 (10.0)
Genitourinary	
Testicular abscess	2 (0.5)
Epididymo-orchitis	16 (4.3)
Central nervous system	
Meningitis	3 (0.8)
Brain abscess	1 (0.2)
Hearing loss	2 (0.5)
Cardiovascular system	
Endocarditis	1 (0.2)
Skin	
Maculopapular rash	1 (0.2)
Ptyriasisrosea	1 (0.2)
Erythema nodosum	1 (0.2)

Table 4. Complications according to age group

Complications	> 15 years (n = 24)	15-45 years (n = 208)	< 45 years (n = 138)	p
Hematological	66.7	58.2	56.5	0.446
Osteoarticular	33.3	44.2	57.2	**0.005**
Organomegaly	58.3	37.5	39.1	0.366
Hepatobiliary	29.2	27.4	25.4	0.616
Gastrointestinal	16.7	10.1	8.7	0.315

Discussion

Brucellosis exists in animals worldwide but is especially prevalent in the Mediterranean basin, the Arabian peninsula, the Indian subcontinent, and in parts of Central Asia, Africa, Mexico, and Central and South America [1]. The incidence of brucellosis in Turkey has been reported to be 1% to 26.7% in various studies, with changing ratios in different regions [8-11].

This study was conducted in a region of Turkey in which brucellosis is seen as an endemic infection. A study population of 370 patients with brucellosis was obtained by analyzing patient files. Just over half (56.2%) of the patients were female. In five different studies conducted in the regions with endemic brucellosis, the female ratio has been reported to be 52%-73%, similar to our results [2,12-15]. In Turkey, increased frequency of the disease in women can be explained by the fact that women are usually responsible for small cattle raising and overseeing dairy production. The mean age of the patients was 39.6±18.2 years in our study, similar to many previous studies [2,16-18]. Some studies, however, reported older mean ages (44-45 years) [12,14]. This age group usually works in farms and deals with dairy production; as a result, the disease is seen more frequently in this age group. The disease is also seen mostly in rural areas where contact with animals is more frequent and food hygiene is poor [19]. However, 50.4% of our patients lived in the city; this may be explained by migration from the countryside.

Family history was positive in 22% of the patients. In previous studies from Turkey and a study from Iran, family history was found to be positive in 9.6% and 54% of subjects, respectively [5,20-22]. These various results may be related to the region of the study. Since the disease is contagious between family members, family members of patients with brucellosis must be investigated.

The probable route of infection was not known in 44.5% of the patients. In 75.6% of 205 patients with a reported probable route of infection, unpasteurized dairy products were found to be the probable route of infection. In previous studies conducted in Turkey, the ratio of contagion from milk and dairy products was reported to be 31%-81% [5,20,22].

The diagnostic serum agglutination test was above 640 in 61.8% of the patients. CRP values during the diagnosis were high in 69.1% of the patients in our study. This ratio is lower compared to other studies that reported high CRP levels at diagnosis [2,13,15,18].

In this study, 70.5% of patients had acute brucellosis, 19.7% had subacute brucellosis, and 9.7% had chronic brucellosis. Similar to our results, previous studies have reported greater numbers of patients in the acute phase [12,-14,16-18,22,23].

Brucellosis may cause nonspecific symptoms such sweating, weakness, and loss of appetite [24]. In studies analyzing the symptoms of brucellosis, fever (59%-91.8%), sweating (15%-92.9%), back pain (28%-61%), headache (5%-64%), loss of appetite (1%-73%), joint pain (34%-84%), myalgia (12%-60%), and weakness (35%-80%) have been reported [25-29]. Similar to Aygen *et al*.'s study [12], the most frequent symptom was found to be weakness. This was followed by fever (63.2%), sweating (62.7%), and arthralgia (59.1%).

Brucellosis complications are a major medical problem in countries where brucellosis is still endemic. These complications include osteoarticular, gastrointestinal, hematological, genitourinary, cardiovascular, respiratory, and central nervous system involvement [28]. Although osteoarticular complications are usually the most frequently occurring complications of brucellosis, the most frequent complications in our study were hematological complications (58.1%), similar to the study of Mermut *et al*. [23]. This was followed by osteoarticular (48.3%), hepatobiliary (26.7%), gastrointestinal (10%), and genitourinary (4.8%) complications.

Although hematological changes are common in brucellosis, they regress easily with treatment.

Anemia, leukopenia, and lymphomonocytosis are frequently seen hematological disturbances, whereas leukocytosis, neutropenia, thrombocytopenia, hemolytic anemia, and pancytopenia are rarely seen [21]. Brucellosis should be considered a possible cause of febrile neutropenia, especially in endemic areas.In various studies, different ratios ofanemia (41%-74%) [23,24], leukopenia (30%-68%) [19,30], and thrombocytopenia (28%-40%) [23] have been reported. In accordance with other studies, anemia was the most frequent hematological change found in our study. We also found leukopenia (21.3%), leukocytosis (9.1%), and thrombocytopenia (22.9%) in patients with brucellosis. Previous studies revealed different frequencies of hematological complications. Sathyanarayanan *et al*.[31] reported anemia in 57.3%, leukopenia in 14.7%, leukocytosis in 14.7%, and thrombocytopenia in 33.8% of patients. Roushan *et al*. [18] reported anemia in 15.1%, leukocytosis in 12.2%, leukopenia in 3%, and thrombocytopenia in 3.4% of 469 patients. Pancytopenia has been found in 0.9%-21% of patients in different studies [2,32-35]. There are conflicting data about the frequency of pancytopenia in different subgroups of the disease. In our study, we found that it is more frequent in acute cases as compared to other groups. However, Gur*et al*. [17] found no difference between clinical forms of the diseases and frequency of pancytopenia in brucellosis. Similar to our results, Buzgan*et al*. [2] reported that pancytopenia was more frequent in acute cases (7%) compared to subacute (1.8%) and chronic (0.7%) cases.

Buzgan*et al*.also reported serious hematological involvement in 1.7% of the patients [2]. Moreover, Ertek *etal*. [36] reported thrombophlebitis in 0.9% of patients, and Colmenero *et al*. [34] reported 0.7% DIC in their study. In our study, however, no serious hematological involvement was found.

Hepatic involvement is common in brucellosis [1]. Hepatomagaly was present in 13.5% of the patients in our study; this ratio is lower compared to previous studies [12,16,34]. AST and ALT was found to be high in 27.5% and 21.6% of the patients, respectively. Similarly, increased liver enzymes have been reported by Buzkan *et al*. in 24.8% of patients [2].

Previous studies have reported the ratio of osteoarticular complications to be between 19%-69% [2,12,13,15,18,34,37]. In this study, 179 of patients (48.3%) developed osteoarticular complications. Ertek *etal*. [36] and Gur *et al*. [17] reported higher ratios of osteoarticular involvement (68.1% and 69%, respectively) than we did in our study. Similar to our findings, Turan *et al*. [37] and others reported 43.7% and 46.5% osteoarticular involvement, respectively [15,23]. In these studies, spondylodiscitis was the most frequent osteoarticular complication, similar to previous studies [15,22,23]. In some studies conducted in Turkey, however, sacroileitis or peripheric arthritis was found to be the most common form of osteoarticular involvement [17,37]. In our study, spondylodiscitis was found in 108 of 179 patients with osteoarticular involvement, and sacroileitis was found in 51 cases. Two of 13 patients who developed paravertebral abscesses needed surgical treatment. Sacroileitits recurred in five patients during the course of the disease. Comparing osteoarticular involvement in the different age groups, osteoarticular involvement was found to occur more frequently in the older age group. In the study of Gur *et al*.[17], sacroileitis and peripheric arthritis was seen more frequently between the ages of 15 and 45 years. In Kursun *et al*.'s study [22] spondylodiscitis was detected in the older age group. Similar to our study, Turan *etal*. [37] found that osteoarticular involvement was seen more frequently in the older age group.

Genitourinary complications have been reported in 2%-40% of patients with brucellosis, and the most frequent one is epididymoorchitis [1,2,17,23]. In our study, orchitis developed in only 16 (4.3%) patients with brucellosis. One patient needed surgical intervention, and recurrence was observed in one patient twomonths after treatment. Abscess formation secondary to brucellosis should therefore be kept in mind in differential diagnosis of testicular masses in young men.

Neurological involvement of CNS was detected in 2%-5% of patients with brucellosis [12,33]. Acute or chronic meningitis is the most common manifestation of neurobrucellosis, but meningoencephalitis, brain abscess, epidural abscess, demyelinating disorders, and meningovascular syndromes have also been reported [38]. We found meningitis in three cases (0.8%) and a brain abscess in only one patient. Neurobrucellosis frequency in our study was similar to that reported by Roushan *et al*. [18] (1.4%), but lower than the ratios reported in other studies [2,12,15,17,18,31]. Although the mortality rate is very low, some sequella may develop despite appropriate therapy in patients with neurological involvement. In our study, partial hearing loss developed in two of the patients with neurological complications.

Endocarditis occurs in less than 2% of cases, but it accounts for the majority of brucellosis-related deaths. Before effective therapy, including valve replacement

surgery, Brucella endocarditis was nearly fatal. The aortic valve is the valve most often involved, and both native and prosthetic valvular infections, as well as infections of other vascular prostheses, have been reported [1].

Colmenero *et al*. reported endocarditis in 1.5% of 530 patients with brucellosis in their study, while Sathyanarayan *et al*. reported an endocarditis ratio of 2.3% [31,34]. The ratio of endocarditis was 0.2% in our study. This low ratio may be explained by the fact that because it is an endemic disease in this region, acute findings of brucellosis are well known, and treatment is started in earlier stages of the disease.

Cutaneous manifestations are not specific [1]. In this study, skin involvement was found in three cases (0.6%). These included erythema nodosum, pitriasisrosea, and maculopapular rash.

Although this study was conducted hospital-based, the generalization of the results would be misleading since the hospital databases of the largest two hospitals were used. This is because the hospitals where the study was conducted are small scale and not centric hospitals. Due to this reason, there may be patients who would not refer to the hospitals. Therefore, like in every hospital-based study, the probable bias should be kept in mind.

Another restriction ofthis study is the fact that the acquired data was restricted with the registrations. As an example, the erythrocyte sedimentation rate data was obtained from only 38% of patients registered in the study; therefore, we were not able to analyze the data according to this parameter. We were not able to obtain data about the progression of disease and the results of treatment because after diagnosis, patient follow-up waslimited or not recorded.

Conclusion

Brucellosis is a common disease that may be accompanied by serious complications. In endemic regions of brucellosis, people should be taught to avoid unpasteurized dairy products. Hematological abnormalities occurring during the course of the disease may be misdiagnosed hematological malignancies. Clinicians must be aware of multiple system involvement in brucellosis, especially hematological and musculoskeletal systems. Osteoarticular complications should be investigated in older patients with brucellosis.

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