

Clinical manifestations, complications, and treatment of brucellosis: evaluation of 72 cases

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Aim: Brucellosis is an important disease in developing countries. We aimed to determine the epidemiologic, clinical, and laboratory characteristics of brucellosis, which still has a high morbidity in Turkey.

Materials and methods: Seventy-two patients with brucellosis, monitored at our clinic from January 2004 to July 2010, were reviewed retrospectively.

Results: The average age was determined to be 44.8 ± 18 years, and 40 of the patients were female (55.6%). The most frequent transmission route was the use of raw milk and dairy products, in 45 of the patients (62.5%). The most frequent complaints were joint pain, high fever, weakness, low back pain, and gastrointestinal symptoms, whereas the most frequent physical examination findings were fever, osteoarticular involvement, splenomegaly, hepatomegaly, and lymphadenopathy. All of the patients were positive for Rose Bengal testing. The standard tube agglutination titer was 1/160 or higher in 64 (88.9%) patients. *Brucella melitensis* was isolated from blood cultures of 13 (18.1%) patients and bone marrow cultures of 7 (9.7%) patients. Complications of sacroiliitis in 6 (8.3%), spondylodiscitis in 4 (5.6%), endocarditis in 2 (2.8%), neurobrucellosis in 1 (1.4%), and epididymo-orchitis in 1 (1.4%) of the patients were observed.

Conclusion: Brucellosis has various clinical presentations. It should be included in the differential diagnosis of high fever and joint pains in endemic countries.

Key words: Brucellosis, clinical manifestations of brucellosis, complications of brucellosis

1. Introduction

Brucellosis is a zoonotic disease caused by *Brucella* spp. (1). Human brucellosis remains the most common zoonotic disease worldwide, with more than 500,000 new cases annually. Its prevalence is more than 1/10,000 in the populations of some endemic countries (2). Although it can be seen in any part of the world, the disease is hyperendemic in the Mediterranean region consisting of Portugal, Spain, southern France, Italy, Greece, Turkey, and North Africa countries, as well as in the Arabian Peninsula, India, Mexico, and Central and South America (2,3). Brucellosis has been eradicated in England, in many northern European countries, and in Australia, New Zealand, and Canada (2). The prevalence of brucellosis in Turkey has been reported to be in the range of 1% to 26.7%, depending on the geographical region (4).

The transmission route is through direct or indirect animal contact. In particular, farmers, shepherds, veterinarians, butchers, and laboratory personnel are at risk of this infection (5). The disease typically takes hold

in young and middle-aged adults. It has a lower incidence in childhood and the elderly (6). Although brucellosis is more prevalent in men due to occupational risk in countries with a low incidence of the disease, it is known that there is no sex difference in countries where it is endemic (3).

Human brucellosis is a multisystemic disease with a broad spectrum of symptoms, although it can be asymptomatic as well. Brucellosis begins as a flu-like disease with symptoms such as fever, headache, malaise, back pain, myalgia, and generalized aches. Splenomegaly; hepatomegaly; gastrointestinal signs such as anorexia, nausea, vomiting, diarrhea, and constipation; coughing; and pleuritic chest pain can be seen. The most common complications are arthritis, spondylitis, epididymo-orchitis, and chronic fatigue. Endocarditis is one of the most serious complications of brucellosis. Some other organs are also affected, resulting in lymphadenopathy, deep vein thrombosis, granulomatous hepatitis, osteomyelitis, anemia, thrombocytopenia, and nephritis (6).

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In the present study we aimed to describe some demographic, epidemiologic, clinical, and laboratory characteristics of patients with brucellosis in Turkey, which is an endemic area for brucellosis, which still has high morbidity.

2. Materials and methods

This study evaluated 72 brucellosis patients hospitalized and monitored at the Clinic for Infectious Diseases and Clinical Microbiology in İzmir Tepecik Education and Research Hospital from January 2004 to July 2010. The information pertaining to the patients was obtained through retrospective examination of the follow-up forms and patient records. The brucellosis diagnosis was made through clinical symptoms and findings, standard tube agglutination test, and/or isolation of *Brucella* spp. in clinical specimens including blood and bone marrow. Significant titers were determined to be $\geq 1/160$ in the standard tube agglutination test (STA) (7).

An automated blood culture system (the BacT/ALERT 3D system, bioMérieux, Durham, NC, USA) was used for isolation of *Brucella* spp. from blood and bone marrow specimens. A Vitec 2 compact system (bioMérieux, Marcy l'Etoile, France) was used for identification and antibiotic susceptibility. Routine laboratory tests were done, including complete blood count, erythrocyte sedimentation rate, C-reactive protein levels, liver profiles including aspartate aminotransferase and alanine transaminase, renal function profiles, and urine examination.

The data were statistically analyzed using SPSS 18.0.

3. Results

In this study, 72 brucellosis patients were reviewed. Of the patients, 40 (55.6%) were female. The mean age was 44.8 ± 18 (range: 14–83). Twenty-eight patients (38.9%) were from rural regions and 44 (61.1%) were from the city center. The most prevalent transmission routes were identified as the use of raw milk and dairy products in 45 of the patients (62.5%), stockbreeding in 27 (37.5%), and consumption of raw milk and dairy products in conjunction with stockbreeding in 18 (25%) patients. Household contact was observed in 5 (6.9%) of the patients. Among the patients included in the study, the most frequently presented complaints were high fever, joint pain, weakness, low back pain, and gastrointestinal complaints (lack of appetite, abdominal pain, and vomiting) (Table 1).

The most frequently observed findings in physical examination of the patients were high fever, osteoarticular involvement, splenomegaly, hepatomegaly, and lymphadenopathy (Table 2).

All of the patients tested positive in Rose Bengal testing (+), whereas 64 (88.9%) had 1/160 titers or higher for the Wright test. *Brucella* spp. was isolated from blood cultures

Table 1. Most frequent complaints.

Symptoms	Number (%)
Joint pains	27 (37.5%)
High fever	26 (36.1%)
Low back pain	19 (26.4%)
Weakness	17 (23.6%)
Headache	9 (12.5%)
Lack of appetite	9 (12.5%)
Abdominal pain	7 (9.7%)
Nausea and vomiting	7 (9.7%)
Sweating	7 (9.7%)
Loss of weight	2 (2.8%)
Pain and edema in testes	1 (1.4%)

Table 2. Most frequently identified clinical findings and complications

Clinical findings and complications	Number (%)
Clinical findings	
Fever	28 (38.9)
Splenomegaly	10 (13.9)
Lymphadenopathy	5 (6.9)
Hepatomegaly	4 (5.6)
Complications	
Sacroiliitis	6 (8.3)
Spondylodiscitis	4 (5.6)
Endocarditis	2 (2.8)
Neurobrucellosis	1 (1.4)
Epididymo-orchitis	1 (1.4)

of 13 (18.1%) patients and from the bone marrow of 7 patients (9.7%). All isolates were identified as *Brucella melitensis*.

Out of the patients, significant anemia was detected in 28 (38.8%) and high serum transaminase levels in 20 (27.8%). Fourteen (19.4%) patients presented with complicated diseases, including sacroiliitis in 6 (8.3%), spondylodiscitis in 4 (5.6%), endocarditis in 2 (2.8%), neurobrucellosis in 1 (1.4%), and epididymo-orchitis in 1 (1.4%). Systematic findings are shown in Table 3.

Table 3. Systematic findings of the patients.

Systematic findings	Number (%)
Hemopoietic system	
Anemia	26 (36.1)
Leukopenia	3 (4.2)
Leukocytosis	4 (5.6)
Thrombocytopenia	5 (6.9)
Gastrointestinal system	
Increased serum transaminase levels	20 (27.8)
Osteoarticular	
Sacroiliitis	6 (8.3)
Spondylodiscitis	4 (5.6)
Genitourinary system	
Epididymo-orchitis	1 (1.4)
Cardiovascular system	
Endocarditis	2 (2.8)
Central nervous system	
Neurobrucellosis	1 (1.4)

The patients were treated with various combinations of antibiotics depending on clinical presentation, drug side effects, and tolerability. The antibiotics were administered for at least 6 weeks; in the case of spondylodiscitis, neurobrucellosis, or endocarditis and for those with therapeutic failure, the duration of treatment continued for up to 1 year. Out of the patients, 42 (58.3%) received doxycycline (200 mg/day orally) plus rifampin (600 mg/day orally) treatment, whereas 19 (26.4%) received doxycycline (200 mg/day orally), rifampin (600 mg/day orally), and streptomycin (1 g/day intramuscularly for 3 weeks); 4 (5.6%) received doxycycline (200 mg/day orally), rifampin (600 mg/day orally), and ceftriaxone (2 g/day intravenously/intramuscularly); 3 (4.2%) received doxycycline (200 mg/day orally), rifampin (600 mg/day orally), and levofloxacin (500 mg/day orally); 3 (4.2%) received doxycycline (200 mg/day orally) and streptomycin (1 g/day intramuscularly for 3 weeks); and 1 (1.4%) received ciprofloxacin (500 mg twice a day orally) and streptomycin (1 g/day intramuscularly for 3 weeks).

4. Discussion

Among high-risk patients in the eastern part of Turkey, seropositivity has been reported to be as high as 27.2% (8). However, the true rates of brucellosis in endemic countries

are most probably higher than reported due to deficiencies in its diagnosis or recording (9).

Brucellosis affects the productive age group, thus leading to significant morbidity and economic losses, particularly in endemic countries such as Turkey (10). In various studies conducted in Turkey, the mean age of patients with brucellosis was seen to range between 33 and 46.7 years (11–13). In this study, the mean age was identified as 44.8 years and found to be concordant with other studies. Although brucellosis is more prevalent in men due to occupational risk in countries with a low incidence of the disease, it is known that there is no sex difference in countries where it is endemic (14). Out of the patients, 40 (55.6%) were female in this study.

As brucellosis is a disease transmitted through animals and animal products, it is seen more frequently in rural areas. Various studies conducted in Turkey demonstrated that most of the patients with brucellosis presented from rural areas (15–17), whereas, in the present study, 28 (38.9%) of the patients presented from a village and 44 (61.1%) were from the city center. We believe that this may be attributed to high immigration into İzmir Province and the connections of the individuals living in urban regions with those from rural areas.

Consumption of raw dairy products such as raw milk and fresh cheese, contact with animals, and contact in the laboratory environment are the dominant risk factors for brucellosis (1). In Turkey, the main transmission source for brucellosis is consumption of unpasteurized milk and dairy products, as is the cases in other countries where the disease is endemic (3). In our study, the consumption of raw milk and dairy products was the case in 50 (69.4%) of the patients. No laboratory-originated transmission was found. Household contact can be observed due to factors such as common dietary habits and contact with animals. In this study, household contact was observed in 5 patients (6.9%).

Brucellosis may present with various symptoms (1). The patients most frequently present with complaints of high fever, weakness, sweating, joint pains, and lack of appetite (3,6). Among the patients included in this study, the most frequently observed complaints were high fever, joint pain, weakness, low back pain, and gastrointestinal complaints (lack of appetite, abdominal pain, and vomiting). Therefore, it is believed that brucellosis should be included in the differential diagnosis of patients with complaints of high fever and joint and low back pain. Physical examination findings also vary depending on the organs involved, and the most common clinical finding is reported as fever (1). In the physical examination of the present study, high fever, joint findings, splenomegaly, hepatomegaly, and lymphadenomegaly were detected. *Brucella* epididymo-orchitis was diagnosed in one patient who presented the complaint of swelling in the testes.

The specific diagnosis of brucellosis is made upon isolation of *Brucella* spp. in samples such as blood, bone marrow, cerebrospinal fluid, synovial fluid, peritoneal and pleural fluid, and sperm, or through the presence of titers of 1/160 and higher in a standard tube agglutination test in the presence of the appropriate clinical presentation (6). Since *Brucella* spp. grows relatively slowly and to culture the organisms is difficult, the standard tube agglutination test is considerably more reliable in the diagnosis of brucellosis when evaluated together with a consistent clinical presentation (18). In the present study, while Rose Bengal test positivity was detected in all of the patients, the standard tube agglutination test was detected positive at 1/160 and higher in 64 (88.9%) of the patients. In the study by Buzgan et al., the STA test was positive in 967 (94.1%) cases, with titers ranging from 1/160 to 1/163. Forty-nine cases (4.8%) that had a negative STA were found to be positive by Coombs STA. Twelve cases (1.2%) were seronegative with a negative agglutination test (11).

The isolation of *Brucella* spp. from blood, bone marrow, or other clinical specimens is required for a definite diagnosis. However, due to the sensitivity of blood culture methods it varies between 15% and 70% (19). Thus, clinicians often rely on the indirect diagnostic tests of brucellosis (20). *Brucella* spp. was isolated in blood and bone marrow samples from 13 (18.1%) and 9 patients (12.5%), respectively. Significant anemia was detected in 28 (38.8%) of the patients. Liver involvement is common in brucellosis. However, transaminase levels may be normal or there may be a mild increase (6). In this study, serum transaminase levels were detected as high in 20 (27.8%) patients.

In conclusion, brucellosis remains a disease with high morbidity in Turkey. As can be observed in various clinical presentations, brucellosis should be included in the differential diagnosis in patients with high fever and joint pain who have the risk factors in endemic countries.

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