BRUCELLOSIS: A RETROSPECTIVE EVALUATION OF 170 CASES

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Abstract

Brucellosis is an important disease with devastating outcomes in developing countries and may cause complications in many organ systems. The clinical and laboratory characteristics of 170 cases of brucellosis followed at the Afyon Kocatepe University Faculty of Medicine Infectious Diseases Clinic and Afyonkarahisar State Hospital of Medicine Infectious Diseases Clinic in Turkey, were retrospectively evaluated. In our study, total of 170 patients (female, n=74; 43.5%, and male, n=96; 56.5%) with a mean age of 44.12 ± 15.52 years were included. The patients were living in rural areas (n=134; 78.8%) or in the city center (n=36; 21.2%), while 112 (65.9%) patients were raising livestock and 84 patients (49.4%) were consumers of unpasteurized raw milk and dairy products. The most frequent complaints detected in patients with brucellosis include joint pain, fever, weakness, back pain and gastrointestinal symptoms. Fever, arthritis and scrotal swelling were observed more frequently than the others. The standard tube agglutination titer was > 1/160 in 150 (88.2%) patients. Blood cultures have positive results in 68 (59.6%) patients. Complications were detected in 45 patients (26.4%). Osteoarticular system involvement was the most common complication in 33 (19.4%) patients. Other complications were epididymo-orchitis in 9 (5.3%) and depression in 3 (1.8%) patients (Table 2). Sacroileitis was the most frequent osteoarticular involvement which was detected in 13 (7.6%) patients. Other osteoarticular involvements were peripheral monoarthritis in 11 (6.5%), and spondylodiscitis in 9 (5.3%) patients. Increased C-reactive protein (CRP) and high serum transaminase levels were significantly higher in the complication groups. The most frequent drug treatment was rifampicin and doxycyline among different treatment regimens. Brucellosis should be considered in the differential diagnosis of patients who present with fever and osteoarticular symptoms. Laboratory results can help the clinician to identify the complications of this disease, especially osteoarticular complications.

1. Introduction

Brucellosis is a zoonosis caused by species of Brucella that can involve various tissues and systems in humans and leads to different clinical pictures (Franco et al., 2007). The incidence of brucellosis in the world varies from less than 0.03 to 160 per 100.000 population. Brucellosis is most commonly seen in the countries of the Mediterranean Region including Africa, Portugal, India, Italy, Greece, and Turkey (Gul and Erdem, 2015). The transmission route is through direct contact with infected animals or consumption of unpasteurized milk and milk products obtained from infected animals (Kursun et al., 2013).

Clinical and laboratory features of brucellosis tend to vary, as the disease is a systemic infection, in which any organ of the body can be involved. Diagnosis of brucellosis is difficult due to the nonspecific signs and symptoms of the disease. Initial symptoms of brucellosis resembles those of gripal infection which include fever, headache, weakness and myalgia. Brucellosis is also charactarized by frequent organ-based complications. The most common complications are arthritis, sacroileitis, epididymoorchitis, spondylodiscitis, arthritis, hepatitis and depression (Gul and Erdem 2015).

In the present study we aimed to retrospectively evaluate the clinical characteristics, laboratory findings, complications and treatment outcomes of patients with brucellosis followed up and to compare these data with those reported in the literature.

2. Material and Method

In this study we evaluated 170 inpatients with brucellosis hospitalized and followed up at the Afyon Kocatepe University Faculty of Medicine Infectious Diseases Clinic and Afyonkarahisar State Hospital of Medicine Infectious Diseases Clinic, Turkey. Follow-up forms and patient records of the patients were retrospectively analyzed to gather information about the demographic characteristics, presenting complaints, physical examination results, hematological and biochemical parametres including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) complete blood count and hepatic function test results at the time of diagnosis. Brucella standard tube agglutination (STA) test results, body temperature, results of blood cultures, therapy combinations and duration of and response to therapy were recorded on brucellosis follow-up forms. The diagnosis of brucellosis was made based on clinical symptoms and findings, STA tests and/or isolation of Brucella spp. in the cultures of clinical specimens. In the STA test results at ≥1/160 titers were considered to be significant (Young EJ, 2010; Al Dahouk S and Nöckler K, 2011). The patients were treated with various combinations of antibioticsaccording to the World Health Organization (WHO) guidelines. The data were statistically analyzed using SPSS 22.0 (Statistical Package for the Social Sciences) statistics program.

3. Results

A total of 170 patients (female, n=74; 43.5% and male, n=96; 56.5%) with a mean age of 44.12 ± 15.52 years were included in the study. The patients were living in rural areas (n=134; 78.8%) or in the city center (n=36; 21.2%), while 112 (65.9%) patients were raising livestock and 84 patients (49.4%) were consumers of unpasteurized raw milk and dairy products.

The number of patients peaked during the summer and spring months. Sixty-seven (39.4%) patients were admitted in the summer and 45 (32.4%) in the spring months.

In our study, the most frequently reported complaints were weakness, high fever, joint pain, sweating, back pain and gastrointestinal complaints (lack of appetite, abdominal pain, and vomiting). Physical examination of the patients most frequently revealed fever, arthritis and scrotal swelling (Table 1).

Table 1. Most frequent complaints and clinic findings

Complaints	Number (%)
Weakness	117(68.8%)
High fever	112(65.9%)
Joint pains	99(58.2%)
Sweating	99(58.2%)
Low back pain	89(52.4%)
Lack of appetite	75(44.1%)
Chills	55(32.4%)
Nausea and vomiting	36(21.2%)
Scrotal pain	11(6.5%)
Abdominal pain	6(3.5%)
Maculopapular rash	3(1.8%)
Clinic findings	Number (%)
High fever	82(48.2%)
Arthritis	13(7.6%)
Scrotal pain and swelling	9(58.2%)
Maculopapular rash	1(0.6%)

STA testing was positive in 150 patients (88.2%). Blood cultures were obtained from 114 patients at admission, and 68 of them (59.6%) were positive for Brucella spp. One patient had Brucella spp. growth in his synovial fluid, and in his blood culture. STA test results of 3 patients with growth in their blood cultures were below 1:160 titre.

Hematological tests revealed the presence of anemia in 46 (27.1 %), high serum transaminase levels in 47 (27.6 %), leucocytosis in 19 (11.2 %), thrombocytopenia in 19 (11.2 %) and leukopenia in 15 (8.8%), elevated CRP in 130 (76.5 %), and increased ESR in 114 (67.1%) patients. Complications were detected in 78 of 170 patients (45.9%). Osteoarticular system involvement was the most common complication in 33 (19.4%) patients. Sacroileitis was the most frequent osteoarticular involvement and was detected in 13 (7.6%) patients. Other osteoarticular involvements were

peripheral monoarthritis in 11 (6.5%) and spondylodiscitis in 9 (5.3%) patients. Other complications were epididymo-orchitis in 9 (5.3%) and depression in 3 (1.8%) patients. Laboratory findings and complications were shown in Table 2.

Table 2. Laboratory findings and complications

Laboratory findings	Number (%)
Hemopoietic system	
Anemia	46(27.1%)
Leukopenia	15(8.8%)
Leukocytosis	19(11.2%)
Thrombocytopenia	19(11.2%)
Gastrointestinal system	
High serum transaminase levels	47(27.6%)
Complications	**Number (%)**
Osteoarticular	
Sacroileitis	13(7.6%)
Spondylodiscitis	9(5.3%)
Arthritis	11(6.5%)
Genitourinary system	
Epididymo-orchitis	9(5.3%)
Others	
Depression	3(1.8%)
Maculopapular rash	1(0.6%)

The patients with and without complications were compared statistically between the 2 groups as for gender, presence of anemia, leukopenia, leucocytosis, thrombocytopenia, high serum transaminase, ESR and CRP levels and STA positivity. Increases in CRP and high serum transaminase levels were significantly were predominant higher in the group with complications (p < 0.05) (Table 3).

Different combinations of antibiotics in consideration of clinical presentation, drug side effects were used in the treatment of the patients. The antibiotics were applied for at least 6 weeks. Most of the patients (n=146, 85.9%) were treated with a combination of doxycycline and rifampicin. Thirteen patients (7.6%) were given a combination of rifampicin and doxycycline plus streptomycin and 4 patients (2.4%) were treated with a combination of rifampicin and ciprofloxacin. Fifty-four patients were followed up during the treatment period. Treatment was extended up for 8 patients to 24 weeks for 3 and up to 12 weeks because of osteoarticular involvements. Besides 9 patients with epididymo-orchitis received a combination of rifampicin and doxycycline for 6 weeks.

4. Discussion

Brucellosis is one of the most common zoonoses worldwide and still remains endemic in Turkey (Yuce and Alp-Çavuş, 2006). Although the incidence of brucellosis has shown a mild decrease in recent years, Turkey remains among the countries in which the disease is prevalent. According to data from the Ministry of Health of the Republic of Turkey, 7.703 cases with brucellosis were reported in 2010 (Yumuk Z and Callaghan DO, 2012; Erbaydar et al., 2012). However, in endemic countries true incidence rates of brucellosis is most frequently underestimated because of inefficient patient registration system.

Table 3. Comparison of noncomplicated and complicated cases

Properties	Patients Noncomplicated	Patients Complicated	P-value
	N (%)	N (%)	
High Fever	59(64.1%)	53(67.9%)	0.601
Anemia	22(23.9%)	26(12.9%)	0.316
Leukopenia	8(8.7%)	7(9.0%)	0.949
Leukocytosis	8(42.1%)	11(14.1%)	0.265
Thrombocytopenia	8 (8.7%)	11(14.1%)	0.265
High serum transaminase levels	0(0.0%)	47(60.3%)	0.000
Elevation of ESR	60(65.2%)	54(69.2%)	0.579
Elevation of CRP	63(68.5%)	67(85.9%)	0.008
STA positive	83(90.2%)	67(85.9%)	0.384

In endemic countries such as Turkey generally productive age group contract the disease resulting in, significant morbidity and economic losses. So Brucellosis may adversely affect the labor force. The mean age of the patients with brucellosis in Turkey was reportedly range between 33 and 46.7 years (Aygen et al., 2002; Demiroğlu et al., 2007). In our study, the mean age of the patients was 44.12 ± 15.52 years and found to be in compliance with other studies. Most of the studies have shown similar gender involvement in brucellosis, however only small number of studies have demonstrated higher incidence rates in among male

patients (Gür et al., 2003). Our study population consisted mostly (n=96; 56.5%) of male patients.

In Turkey most cases of brucellosis onset in the spring and summer months as is seen in other endemic areas of the world (Gul and Erdem, 2015; Doğanay and Meşe, 2008; Hasanjanı et al., 2004; Uluğ and Uluğ, 2010). Increased consumption of unhealthy milk, milk products, and also ice creams during the hot summer months may be held responsible for the higher incidence of brucellosis seen during this period. Since brucellosis is transmitted primarily by consumption of unpasteurized dairy products and by direct contact with animals

apparently it is seen more frequently among people living in rural areas (Demirtürk et al., 2008; Buzgan et al., 2010; Gonen et al., 2014; Naz et al., 2009; Vançelik et al., 2008).

Consistent with the literature, in the present study, 134 (78.8%) patients were referred from a rural area and 36 (21.2%) patients from the city center.

Brucellosis is a systemic infection that can lead to various clinical symptoms; therefore, the signs and symptoms are usually not specific to the disease. Joint pain, fever, weakness, sweating and back pain are the most common symptoms (Gul and Erdem, 2015; Doğanay and Meşe, 2008). In our study, the most frequently observed clinical complaints were high fever, joint pain, weakness, back pain, and gastrointestinal symptoms (lack of appetite, abdominal pain and vomiting). Similar to our study, in a systematic review of the clinical manifestations of brucellosis, the authors found that the main clinical manifestations are fever, join pain, myalgia, and back pain (Dean et al., 2012). Physical examination findings also vary depending on the organs involved, and the fever is the most frequently reported clinical finding (Gul and Erdem, 2015, Doğanay and Meşe, 2008). In the study, physical examination such as high fever, arthritis and scrotal swelling were detected.

Brucellosis may progress with complications that involve many tissues and organs. Osteoarticular infection is the most frequent complication of brucellosis and its prevalence varies between 10% to 80% in several studies (Buzgan et al., 2010; Calık and Gokengin, 2009; Bulut et al., 2011). We identified osteoarticular complication 19.4% of our patients. Osteoarticular system findings include sacroileitis, peripheral arthritis, spondylodiscitis, osteomyelitis and bursitis. In our study, sacroileitis was the most frequent osteoarticular involvement which was detected in 13 patients (7.6%). Urogenital system involvement is encountered in 2-10% of male cases with brucellosis (Gul and Erdem, 2015; Doğanay and Meşe, 2008). In the present study, genitourinary system involvement was the third leading complication with a prevalence rate of 5.3 percent. The specific diagnosis of brucellosis is made based on isolation of the agent from the blood, bone marrow or other tissue cultures (Barua et al., 2016). Blood culture positivity in brucellosis ranges between 15 and 70% (Doğanay and Meşe, 2008; Buzgan et al., 2010). In a review it found that 30 articles including 4681 cases were tested by blood culture 48.3%of cases were positive of Brucella melitensis (Zheng et al., 2018). The diagnosis was based on isolation of the bacteria in blood cultures in 68 (59.6%) of the cases in our study. Brucella spp. grow relatively slowly. Waiting for the culture results may delay the initiation of treatment. As reported in many literature studies titres of ≥ 1:160 in the STA test together with a consistent clinical presentation are more reliable diagnostic biomarkers in brucellosis (Mert et al., 2003; Demirtürk et al., 2008; Buzgan et al., 2010; Kayaaslan et al., 2013). In the present

study STA positivity was found in 150 (88.2%) of our patients (titer ≥1/160).

Anemia, leukopenia, leukocytosis, thrombocytopenia, elevated liver enzymes and increased CRP were the most prominent laboratory abnormalities seen in patients. CRP is an acute phase reactant which is synthesized in hepatocytes, and increases in cases with acute brucellosis (Navarro et al., 1990). Various rates of CRP (36-93%) have been reported in the studies (Demirtürk et al., 2008; Buzgan et al., 2010; Gonen et al., 2014). Elevation of CRP was detected in 130 patients (76.5 %) in our study and it is more than the others. CRP may be used to confirm the diagnosis, and increased CRP is also seen more frequently in patients with complicated cases (Kurtaran et al., 2012; Kayaaslan et al., 2016). Reticuloendothelial system (RES) is affected in cases with brucellosis, and the liver is involved in almost all patients with brucellosis. Hepatic involvement leads to moderate elevation in liver enzymes (Doğanay and Meşe, 2008; Gul and Erdem, 2015). In our study, elevation in hepatic enzymes was observed in 27.6% of the cases.

As Brucella bacteria are facultative intracellular microorganisms, short-term monotherapies cause relapses. So it is necessitate long-term use of at least two drugs in combination. Currently, optimal treatment of uncomplicated brucellosis should be based on a six-week regimen of doxycycline at an oral dose of 2x100 mg/day combined either with streptomycin at an oral dose of 1x1 gr/day for 2–3 weeks, or rifampicin at an oral dose of 2x600 mg/day. Gentamicin may be considered as an acceptable alternative to streptomycin, while all other regimens/combinations should be considered second-line therapy (Ariza et al., 2007). In the present study, the most frequently used therapy option was six weeks of doxycycline and rifampicin combination. Fifty-four patients were followed up during the treatment period. Treatment was extended up to 24 weeks for 3 and up to 12 weeks for 8 patients because of osteoarticular involvements. Besides 9 patients with epididymo-orchitis received a combination of rifampicin and doxycycline for 6 weeks.

In conclusion, brucellosis is still endemic in Turkey and it is a systemic infection with various clinical manifestations and complications. It should be considered in the differential diagnosis of patients who present with fever and osteoarticular symptoms, especially in patients living in endemic regions. Laboratory results can help the clinician to identify the complications of this disease, which progresses with especially osteoarticular complications. Non-specific tests such as CRP should also be used in determine complications. Further research is needed to determine the most appropriate treatment choices and durations in especially complicated brucellosis. In order to prevent this disease, veterinary studies should be performed and necessary precautions should be taken to prevent the use of unpasteurized dairy products.

Conflict of interest

The authors declare that there is no conflict of interest.

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