

Clinical and therapeutic features of brucellosis: An 11-year study at a tertiary care hospital in Riyadh, Saudi Arabia

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Abstract. To study the varying presentations, risk factors, and treatment outcomes among patients with physician-diagnosed brucellosis. This retrospective analysis evaluated all cases of brucellosis reported at King Khalid University Hospital during 2003-2013. Data were retrieved from patient records and a laboratory information system. Descriptive statistics were generated to summarize the study variables. Fisher's exact test or Pearson's chi-square test was used to compare categorical variables. Out of 163 patients identified with brucellosis, 76.7% of patients were culture positive. Fever was the most frequent symptom (85.9%), followed by arthralgia (46.6%). The most common clinical signs was splenomegaly (12.9%), followed by hepatomegaly (11.0%). Laboratory investigations revealed lymphocytosis and anemia in 66.3% and 55.2% of the patients, respectively. Approximately half of the patients (47.8%) had high erythrocyte sedimentation rates, and 56.4% had neutrophilia. Raw milk consumption and direct contact with animals were reported by 45.4% and 16.0% of patients, respectively. Treatment failure and relapse were observed in 8 (5.7%) cases. All treatment failures and relapses occurred among children ≤ 10 years of age or adults > 45 years old (11.0% vs. 0%; $p = 0.006$). Our findings demonstrate that raw milk consumption can be a substantial factor in brucellosis prevention in Saudi Arabia. Laboratory findings, along with the observed pattern in clinical signs and symptoms, can potentially mean underdiagnosis of mild cases. Age was the only factor associated with unfavorable treatment outcomes.

INTRODUCTION

Brucellosis is a major public health problem, especially in the Mediterranean countries, North and East Africa, the Middle East, South and Central Asia and Central and South America. This zoonotic disease is caused by gram-negative *Brucella* species. The disease can be transmitted to humans through direct or indirect contact with infected animals;

their products, such as raw dairy products and infected meat; or their bodily fluids (Corbel *et al.*, 2006). The incidence of brucellosis has been reported to exceed 200 cases per 100 000 in endemic regions (Gwida *et al.*, 2010). The number of reported cases of brucellosis has decreased in Saudi Arabia over the past 10 years, from approximately 5,000 cases per year (22.9 per 100 000) to 3,500 cases per year (12.5 per

100 000), but still requires robust preventive measures to control the disease (Aloufi *et al.*, 2016).

Approximately 90.0% of human brucellosis in Saudi Arabia are caused by *Brucella melitensis*. The consumption of raw, unpasteurized milk from sheep, goats and camels is traditional in Saudi Arabia, and is considered to be the main mode of *Brucella* transmission in the country. Saudi Arabia is a major animal importer, especially during the Hajj season, and the lack of strict control measures have a substantial role in spreading infection (Memish, 2001).

The clinical presentation of brucellosis is non-specific, with mild symptoms in many patients. Thus, this disease is difficult to diagnose while it can involve multiple organ systems of the human body and lead to chronic debilitating and disabling disease with severe complications. Typical symptoms include fever, sweats, fatigue, malaise, anorexia, weight loss, headache, arthralgia and back pain. While the osteoarticular complications of *Brucella* infection are most common, complications can affect any organ system (Corbel *et al.*, 2006).

A recent systematic review commissioned by the World Health Organization concluded that there is a lack of information on the clinical manifestations of brucellosis and patterns of exposure to *Brucella* infection, which prevents policymakers to fight the disease more effectively (Dean *et al.*, 2012). Unfortunately, there are limited published data on human brucellosis in Saudi Arabia as well. To that end, we conducted this study to examine the varying presentations, risk factors, and treatment outcomes among patients with physician-diagnosed brucellosis over a period of eleven years at one of the major tertiary care hospitals in Saudi Arabia.

METHODS

This retrospective study was conducted at the King Khalid University Hospital, Riyadh, Saudi Arabia, which is an 850-bed teaching hospital with a catchment population of

approximately six million people. Data for all brucellosis cases identified from January 2003-December 2013 were abstracted from patient files and the laboratory information system. Patient information collected from the medical histories included demographics, clinical features, laboratory investigations, disease management, treatment outcome, and risk exposure data. Our study has been performed in accordance with the Declaration of Helsinki and the Institutional Review Board of the College of Medicine, King Saud University approved this study.

At the time of a diagnosis, blood culture and serology were performed. Blood culture was performed using the Bac/Alert blood culture detection system (Hemdin, Bio-merieux, France). *Brucella* serology was performed using the standard tube agglutination test (STAT) and micro-agglutination test with the inclusion of albumin to enhance agglutination (Remel Europe Ltd., Kent, UK). All serological tests were performed in accordance with the manufacturer's instructions. Statistical analysis was performed using SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were generated to summarize the study variables. Fisher's exact test or Pearson's chi-square test were used to compare categorical variables.

RESULTS

A total of 163 patients with brucellosis were identified during the period between January 1, 2003, and December 31, 2013. *Brucella melitensis* and *Brucella abortus* were the main responsible agents of brucellosis in our patients. The majority of the patients were males (67.5%), Saudi Arabian (98.2%) and from Riyadh (79.1%). The mean age was 29 years (standard deviation [SD] = 8), and 44.2% of patients were ≤ 20 years of age. Of the patients, 74 (45.4%) reported a history of unpasteurized milk consumption, 26 (16%) had direct contact with animals and 2 (1.2%) had eaten undercooked meat.

Table 1 shows the clinical characteristics of the study population. The majority of

patients (76.7%) were culture-positive. Fever was the most frequent presenting symptom and was present in 140 (85.9%) patients; other commonly reported symptoms included arthralgia (N = 76; 46.6%), malaise and/or fatigue (N = 52; 31.9%), rigor (N = 49; 30.1%), sweating (N = 45; 27.6%), anorexia (N = 40; 24.2%), vomiting (N = 37; 22.7%) and lower back pain (N = 31; 19%). The most common clinical signs detected among the patients were splenomegaly (N = 21; 12.9%), hepatomegaly (N = 18; 11%) and muscle tenderness (N = 13; 8%). Table 1 shows the distribution of presenting symptoms and clinical signs. Sixty-seven patients (41.1%) had co-morbidities, with the most frequent being diabetes mellitus (N = 21; 31.3%) and hypertension (N = 16; 23.8%). Laboratory investigations revealed lymphocytosis and anemia in 66.3% and 55.2% of the patients, respectively. Approximately half of the patients (47.8%) had high erythrocyte sedimentation rate (ESR) levels, and 56.4% had high levels of neutrophils (Table 2).

Outcome data were not available for 23 (14.1%) patients. The majority of the remaining 140 patients made a full recovery (94.3%); however, treatment failure and relapse was observed in 8 (5.7%) patients. All treatment failures and relapses occurred among children \leq 10 years of age or adults $>$ 45 years old, and the frequency of these treatment outcomes was significantly lower in the 11–45 age group (11.0% vs. 0%; $p = 0.006$).

Table 1. Clinical characteristics of the study population

Characteristics	n	%
Unit (n = 163)		
Inpatient	53	32.5
Out-patient	110	67.5
Culture positive	125	76.7
Symptoms (n = 163)		
Fever	140	85.9
Arthralgia	76	46.6
Malaise/fatigue	52	31.9
Rigor	49	30.1
Sweating	45	27.6
Anorexia	40	24.2
Vomiting	37	22.7
Lower back pain	31	19.0
Headache	31	19.0
Abdominal pain	28	17.2
Weight loss	27	16.6
Cough	26	16.0
Myalgia	18	11.0
Diarrhea	14	8.6
Nausea	11	6.8
Sore throat	8	4.9
Constipation	7	4.3
Continuous lesion	1	0.6
Other symptoms	49	30.1
Signs (n = 163)		
Hepatomegaly	18	11.0
Splenomegaly	21	12.9
Lymphadenopathy	5	3.1
Tenderness	13	8.0
Co-morbidities (n = 67)		
Diabetes Mellitus	21	31.3
Hypertension	16	23.8
Heart disease	8	11.9
Rheumatoid arthritis	8	11.9
Liver disease	6	8.9
Others co-morbidities	8	11.4

Table 2. Laboratory findings for patients identified with brucellosis, n = 163

	Low		Normal		High	
	n	%	n	%	n	%
HB	90	55.2	36	22.1	8	4.9
WBC	41	25.2	75	46.0	20	12.3
Platelets	18	13.7	110	84.0	3	2.3
Lymphocytes	1	0.6	4	2.5	108	66.3
Neutrophils	16	9.8	6	3.7	92	56.4
Monocytes	6	3.7	64	39.3	41	25.2
ESR	–	–	34	20.9	78	47.9
ALT	–	–	40	24.5	32	19.6
AST	1	0.6	30	18.4	72	44.2

HB, hemoglobin; WBC, white blood cells; ESR, erythrocyte sedimentation rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

DISCUSSION

The mode of brucellosis transmission varies in different locations most likely due to local practices and cultural differences. In the present study, approximately half of the patients (45.4%) reported a history of consumption of unpasteurized milk. A study conducted in the northern region of Saudi Arabia reported raw milk consumption among 27.0% of investigated patients with brucellosis (Fallatah *et al.*, 2005), whereas the prevalence of this consumption behavior among brucellosis cases in Tabuk province was found to be 88.3% (Elbeltagy, 2001). In accordance with a previous report (Malik, 1997), raw milk consumption continues to be a major risk factor for acquisition of *Brucella* infection in Saudi Arabia. With only 16.0% of patients reporting a history of animal contact, it does not appear to be a strong risk factor in this particular cohort, although the literature reports higher prevalences with animal contact in other regions of Saudi Arabia (Elbeltagy, 2001, Malik, 1997). The nomadic background of the population with high prevalence of raw milk consumption in rural regions has been reported to play a major role in brucellosis transmission in Saudi Arabia (Memish, 2001). Observed differences in raw milk consumption in different geographical regions can be due to the above mentioned differences in the study populations. More studies are needed.

In the present study, the most common manifestations of brucellosis were fever (85.9%), arthralgia (46.6%), malaise (31.9%), and sweating (27.6%). This spectrum of complaints was comparable to that found in previous reports indicating fever as the most common symptom (Andriopoulos *et al.*, 2007). However, a similar study describing brucellosis reported fever in 93.0% of cases, sweating in 82.0% of cases and arthralgia in 78.0% of cases, suggesting that these manifestations may present simultaneously in the majority of patients (Zribi *et al.*, 2009). Hepatomegaly and splenomegaly are among the most frequently reported signs observed in patients with brucellosis. Mantur and colleagues reported hepatomegaly in 11.3% and splenomegaly in 19.2% of patients

(Mantur *et al.*, 2006). Barosso Garsia *et al.* (2012) reported prevalence as high as 74.2% for hepatomegaly and 26.9% for splenomegaly among 1595 patients with brucellosis. In the present study, hepatomegaly and splenomegaly were less frequent and were observed in 11.0% and 12.9% of patients, respectively; however, another study investigating clinical presentations of brucellosis in Saudi Arabia reported hepatomegaly in 46.2% and splenomegaly in 42.3% of patients. The possible reason for the observed differences in the presenting sign and symptoms can be due to high proportion of acute cases in our study population compared to the literature, which can potentially mean underdiagnosis of mild cases (Corbel *et al.*, 2006). Further studies are needed to explore those differences.

Research suggests that some general hematological findings may occur frequently in patients with brucellosis, such as anemia, thrombocytopenia, leukopenia, relative lymphocytosis, and pancytopenia. Patients with brucellosis may also have elevated levels of liver enzymes, which may be a sign of hepatic involvement (Al-Nassir *et al.*). Among our patients, anemia (55.2%), thrombocytopenia (13.7%), leukopenia (25.2%), lymphocytosis (66.3%) and pancytopenia (6.1%) were observed. In addition, our findings showed that a significant number of our patients had high levels of ESR (47.9%) and monocytes (25.2%). These findings are consistent with the literature, as similar results have been reported in other studies (Buzgan *et al.*, 2010, Franco *et al.*, 2007).

While neutrophilia is not characteristic of brucellosis unless the disease is in its initial or disseminated phases (Dale, 2010), 56.4% of our patients had elevated levels of neutrophils. For example, Jiao and colleagues (Jiao *et al.*, 2015) reported neutrophilia in 4.6% of patients. In addition, we had a high prevalence of culture-positive cases (76.7%), which is common in acute cases of brucellosis (Andriopoulos *et al.*, 2007). According to the literature, the proportion of culture-positive cases can vary from 15–70% (Pappas *et al.*, 2005).

Considering the high proportion of patients with neutrophilia and positive culture, along with the observed pattern in clinical signs and symptoms, our findings can possibly indicate that the substantial part of mild brucellosis cases are underdiagnosed and there can be a substantial need to use better diagnostic tools, as well as increasing the awareness of the disease among the general population and physicians, to address this issue. Further studies are needed.

Although, there are no specific treatment protocols for Brucellosis in our hospital, in the present study, the vast majority of patients were treated successfully with antimicrobial therapy composed of doxycycline, rifampicin, streptomycin, tetracycline and trimethoprim/sulfamethoxazole (TMP/SMX) in varying combinations, with relapse and treatment failure rates of 3.6% and 2.1%, respectively. Doxycycline-rifampin and doxycycline-streptomycin were the most commonly prescribed drug regimens for adults and children older than 8 years, and rifampin-sulfamethoxazole-trimethoprim for children younger than 8 years old. The findings of a recent systematic review by Alavi *et al.* (2013), who compared different studies with different combinations of antimicrobial therapies for brucellosis, suggest that the relapse and treatment failure rates found in our study are relatively low. In our study, age was the only factor associated with unfavorable treatment outcomes, as relapse and treatment failure only occurred among children ≤ 10 years of age or adults > 45 years old. We did not find any association between drug regimens and treatment outcomes and think that our findings can be the result of poor adherence to prescribed medications. Further studies are needed to determine potential reasons for the observed age distribution of relapse and treatment failure.

One of the limitations of this study was its retrospective design, which restricted us from having more detailed clinical and epidemiological patient information. The study was conducted only at King Khalid

University Hospital in Riyadh, which could limit the generalizability of our findings.

In conclusion, our findings demonstrate that raw milk consumption can be a substantial factor in brucellosis prevention in Saudi Arabia. Age was the only factor associated with unfavorable treatment outcomes in our study, as relapse and treatment failure only occurred among children ≤ 10 years of age or adults > 45 years old. High proportion of patients with neutrophilia and positive culture results, along with the observed pattern in clinical signs and symptoms, can possibly indicate underdiagnoses of mild cases of brucellosis. Further studies are needed.

Declaration of interest

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