

***Brucella* Bacteremia in Pediatrics Age Group: Experience at King Fahad Medical City in Riyadh, Saudi Arabia**

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Abstract

Introduction: Brucellosis is a zoonotic disease that is common worldwide; it is caused by gram-negative coccobacilli of the *Brucella* genus. Although it is assumed that children are not commonly affected, several reviews from multiple endemic areas have revealed a high percentage of pediatric patients with broad clinical manifestations. This study aims to evaluate the clinical presentation, predisposing factors, and the outcome of pediatric patients diagnosed with clinical brucellosis at King Fahad Medical City (KFMC) in Riyadh, Saudi Arabia.

Method: We conducted a retrospective study of all pediatric patients aged 1 month to 14 years who presented to the Children's Specialized Hospital at KFMC with positive blood cultures for *Brucella* spp. between 2007 and 2017.

Result: A total of 39 patients, with documented *Brucella* spp. bacteremia, were included in this review, 29 (74.36%) males and 10 (25.64%) females. A total of 28 (71.79%) patients were diagnosed with acute, sub-acute, and chronic infections. Most patients were originally from Riyadh. Of these cases, only 22 (61.11%) reported a clear history of raw milk consumption. The most frequent symptoms were fever, arthralgia, and abdominal pain. The most frequent clinical findings were splenomegaly (30.65%), hepatomegaly (29.41%), and lymphadenopathy (27.78%). The most common laboratory findings were high IgM (82%), IgG (74%), ESR (69%), and CRP (58%) levels. The serum agglutination test was positive in 20 (28%) cases, with titers of >1:160 in 11 patients. Four patients developed arthritis, while 1 developed osteomyelitis as a complication of brucellosis. Most cases, 20 (87%) were followed-up for at least 4-6 weeks post-treatment and recovered with no sequela.

Conclusion: In our study, the prevalence of brucellosis was higher among male patients who live in Riyadh. Most patients presented with clinical symptoms of acute brucellosis. Raw milk ingestion, contact with animals, and

family history were the major risk factors. Fever was the most common presenting symptom. However, the most common clinical finding was lymphadenopathy with hepatosplenomegaly. Most of our patients had high IgM and IgG along with high inflammatory markers (ESR and CRP), and serum agglutination was positive in most cases.

The diagnosis of brucellosis was confirmed through positive culture results. Some of our patients had arthritis and osteomyelitis as complications during the follow up period. All patients were followed-up for at least 4-6 weeks post-treatment with only few patients that relapsed. Saudi Arabia is still considered to be one of the endemic areas and we highly recommend increasing public awareness about brucellosis and its complications.

Keywords: Brucellosis; Bacteremia; Children; Clinical presentation; Laboratory investigation; Outcome

Introduction

Brucellosis is a zoonotic disease that is common worldwide. It is caused by small, fastidious gram-negative coccobacilli of the *Brucella* genus [1,2]. Brucellosis is still an endemic in some areas of the world [1-6]. It is more common in countries that do not have effective public health and domestic animal health programs. The currently listed high risk geographical regions are: the Mediterranean Basin, Mexico, South and Central America, Eastern Europe, the Caribbean, Africa, Asia, and the Middle East [2].

In Saudi Arabia, the problem became evident in the early 1980s when the disease emerged as a significant public health concern. Unfortunately, Saudi Arabia is still considered to be one of the endemic areas; even though the incidence rates have decreased, they are still higher compared to other developing countries [1].

The disease equally affects adult and pediatric age groups. Although it is believed that children are not commonly involved,

a number of reports from different endemic areas have revealed a high percentage of pediatric patients, who account for 20-30% of affected patients [7,8]. With different endemicity reported throughout the regions of Saudi Arabia, it is higher in rural areas owing to close contact with animals; the disease is more predominant in males [2,9].

Humans are typically infected by direct contact with infected domestic animals (e.g., camels, sheep, cows, goats, and dogs), by consuming their products (e.g., unpasteurized milk/cheese or meat), or through their discharges, which is common among shepherds, farmers, and veterinarians, as has been reported in the literature. Alternatively, infection also spreads by inhalation of infectious aerosols [10,11].

Brucellosis produces a variety of non-specific manifestation such as prolonged fever, arthritis, or generalized weakness [1,2,8]. In addition, many asymptomatic cases have been reported in the literature among pediatric patients [12,13].

In high endemic areas, this disease should be considered as one of the differential diagnosis in any patient presenting non-specific symptoms. Through early diagnosis and effective treatment, many of these patients recover without any persistent complications. However, rare cases of osteomyelitis and neurobrucellosis have been reported in 1%-2% and 0.5%-1% of cases, respectively. Moreover, in children with brucellosis, myocarditis has been reported as a complication of brucellosis [1]. This study aimed to evaluate the clinical presentation, predisposing factors, and the outcome of pediatric patients diagnosed with clinical brucellosis.

Methodology

This study was conducted at King Fahad Medical City (KFMC) Riyadh, Saudi Arabia. In this retrospective descriptive study, we included all pediatric patients aged 1 month to 14 years who presented to the Children's Hospital at King Fahad Medical City with positive cultures of *Brucella* during the period from 2007 to 2017.

Adult patients and patients who were presented and treated as brucellosis cases through the Emergency Department were excluded. Demographic data (i.e., age, sex, and residence), diagnosis, clinical presentation, physical examination, laboratory data, type of antibiotics received, complications and outcome after follow-up for each patient were collected by reviewing patient medical records with the help of Microbiological and Serology Labs in our hospital. Categorical and numerical data were processed and summarized using SPSS 25th edition in cooperation with biostatistician staff from our Research Center. Descriptive analysis was used to conduct this study to describe patients by frequency and proportion for categorical variables such as age and sex. The mean and standard deviation for continuous variables were also determined. Approval was obtained from the Institutional Review Board from our Research Center.

Results

During the study period, a total of 39 patients had documented *Brucella* spp. bacteremia, 29 were male (74.36%) and 10 (25.64%) were female. The mean patients' age was 7.88 years, ranging from 3 months to 14 years of age. A total of 14 (35.90%) patients were 0-5 years old, 11 (28.2%) were 6-10 years old and 14 (35.90%) were 11-14 years old (**Table 1**). Regarding the diagnosis, most commonly, affected children presented acute symptoms, i.e., 28 (71.79%) patients. However, a quarter of children were below the age of 5 years old (**Table 1**).

Most of the cases, 14 (56%), were originally from Riyadh, while 11 (44 %) lived outside Riyadh. In terms of risk factors, only 22 (61.11%) patients reported a clear history of consuming unpasteurized milk and other dairy products, while 12 (34.9%) had a history of direct contact with infected animal secretions or their products. There was a positive family history of brucellosis infection in 13 (37.41%) of the cases. All reviewed cases with positive blood cultures had at least one risk factor.

The most frequent symptoms were fever (97.44%), arthralgia (joint pain) (50.00%), and abdominal pain (18.42%). The most frequent clinical examination findings were splenomegaly (30.56%), hepatomegaly (29.41%), and lymphadenopathy (27.78%) (**Table 1**). The most common laboratory findings were high IgM (82%), IgG (74%), ESR (69%), and CRP (58%) levels. The serum agglutination test was positive in 11 (28%) cases. The *Brucella* spp. growth from blood culture was achieved in all cases with the median time of positive culture of 76 h. Patients were treated with various combinations of antibiotics. The regimens included the following.

The most commonly used regimen for children older than 8 years of age included Doxycycline and Rifampicin, administered orally for a minimum duration of 28 d to the maximum duration of 90 d. For patients who required hospitalization, Gentamicin was given intravenously for a minimum of 2-14 d.

For most patients below 8 years of age, Rifampicin and TMP/SMX (Bactrim) were given orally for a minimum of 8 d (for Bactrim) and 28 d (for Rifampicin) to the maximum duration of 90 d for both drugs.

The least used regimen was Doxycycline and TMP/SMX (Bactrim) for most children older than 8 years of age, administered orally for a minimum duration of 8 d (for Bactrim) and 28 d (for Doxycycline) to the maximum duration of 90 d for both drugs.

All isolates were identified as *Brucella* spp. *In vitro* antibiotic susceptibilities, for Trimethoprim-Sulfamethoxazole (TMP-SMZ), tetracycline, streptomycin, ciprofloxacin, rifampicin, and imipenem against *Brucella* spp. were reported in xx cases. According to the MIC of our cases, tetracycline was determined to be the most active agent, followed by TMP-SMZ (Bactrim), streptomycin, ciprofloxacin, and rifampicin.

Most patients were followed-up. **Table 2** shows the list of complications of brucellosis. Most cases, 20 (87%), were followed-up for at least two weeks post-treatment and recovered with no sequela. The relapse rate among the

followed-up cases was 3 (13%) patients. However, the remaining 19 (45%) cases were lost to follow-up.

Characteristic	Number (%) N=39
Age (years)	
0-5	14 (35.90)
6-10	11 (28.21)
11-14	14 (35.90)
Time of presentation	
Acute	28 (71.79)
Sub-acute	7 (17.95)
Chronic	4 (10.26)
Pertinent history	
Recall of raw milk ingestion	22 (61.11)
Positive family history of brucellosis	13 (37.41)
Direct animal contact	12 (34.29)
Presenting symptoms	
Fever	38 (97.44)
Joint Pain	19 (50.00)
Abdominal pain	7 (18.42)
Headache	6 (16.22)
Myalgia	6 (16.22)
Change in bowel habits	5 (13.51)
Weight loss	5 (13.51)
Night sweat	4 (10.53)
Weakness	3 (8.33)
Back pain	4 (11.11)
Skin Rash	2 (5.56)
Presenting physical signs	
Splenomegaly	11 (30.56)
Hepatomegaly	10 (29.41)
Lymphadenopathy	10 (27.78)
Abdominal distension	8 (22.22)
Joint swelling	8 (22.86)
Skin changes	8 (22.22)
Murmur	5 (13.89)
Presenting lab findings	
Blood culture	39 (100%)
IgM	32 (82.1%)
IgG	29 (74.4%)
WBC	Mean (7941)
ANC	Mean (2661)

Hgb	Mean (11.1)
Platelets	Mean (237)
ESR	Median (31)
CRP	Median (20.45)
AST	Median (43)
ALT	Median (51)
<p>Note: White blood cells (WBC): Leukopenia: less than (<5000 × lob/L), Leukocytosis: more than (>10000 × lob/L)</p> <p>Absolute neutrophils count (ANC): Mild: 1000-1500/μL, Moderate: 1000-500/μL, Severe: <500/μL</p> <p>Hemoglobin (HGB): Anemia: (<10 g/dL)</p> <p>Platelets: (<50,000)</p> <p>Erythrocyte sedimentation rate (ESR): (>25 mm/h)</p> <p>Alanine aminotransferase (ALT): >50 IU/L</p> <p>Aspartate aminotransferase (AST): >50 IU/L</p>	

Table 1 White Blood Cells (WBC).

Complications	No. of patients	Percentage
Osteomyelitis	1	2.4
Arthritis	4	10.26
Pneumonia	0	0
Myocarditis	0	0

Table 2 List of complications of brucellosis.

Discussion

Our study noted that there was a male predominance, which was similar to other reported studies [1,2,4,7,12,13]. By age group, in this study, the mean age of patients admitted as brucellosis cases was 8 years old, which was similar to a study conducted in Iran (the mean age of 6 years old, ranging from 2-14 years old). The youngest patient was a 3 months old infant. However, in a similar study in Bosnia and Herzegovina, the youngest patient was 1 month old [2]. Most patients frequently presented clinical symptoms of brucellosis during the acute phase, which is defined by a duration of <2 weeks. Similar results were found in Saudi Arabia and central Turkey [4]. Our study showed that the prevalence of brucellosis was higher among patients who were resided in Riyadh and resided in suburban or rural areas within the Riyadh region [5,7]. Raw milk ingestion, contact with animals, and family history of brucellosis were the major risk factors, which agrees with similar studies conducted in Saudi Arabia, Iran, and Bosnia and Herzegovina [13]. Although the majority of case studies conducted in Saudi Arabia and central Turkey showed that consumption of unpasteurized milk or dairy products was significantly more common, a study conducted in southwestern Saudi Arabia showed that most cases had a history of direct contact with animals [2,4,5,7,13]. Fever and arthralgia were the most common symptoms, which is similar to other studies conducted in Saudi Arabia, Bosnia and Herzegovina, and central Turkey. Although clinical findings are reported differently in the literature [2,4,7,13]. The most frequent clinical findings in our

study were splenomegaly, hepatomegaly, and lymphadenopathy, which is similar to those reported in studies carried out in Iran and Bosnia and Herzegovina [2,4,5,7,13]. Most of our patients had anemia with high inflammatory markers (ESR and CRP), which is similar to other studies performed in Iran and Bosnia and Herzegovina [2,4]. Serum agglutination test was positive in most of our patients, which is similar to the reports in various studies from central Turkey and different regions of Saudi Arabia [2,4]. All patients were determined to have a positive blood culture result, which we relied upon to establish the diagnosis of brucellosis in our study [5,7]. However, different reports considered positive serum agglutination with the clinical presentation to be sufficient to make a diagnosis in different regions of Saudi Arabia. Almost all of our patients received a combined therapy of two antibiotics for a long period of time [7]. The choice of antibiotic and duration depended on the age of the patient. In a study from Iran, the drug management used was similar to the one used in our study. No deaths were reported in our study [2].

However, few patients had arthritis and osteomyelitis as complications during the follow-up period. Other studies from Bosnia and Herzegovina and central Turkey have reported similar complications [4,5]. All patients were followed-up for at least 4-6 weeks post-treatment; only few patients relapsed. In previous studies as well as in a study from Bosnia and Herzegovina, fewer relapses have been reported [4].

Limitations

This is a retrospective study with all its inherent limitations. One limitation is that the study included only patients who were presented at King Fahad Medical City. Another limitation is that this study was conducted in the Riyadh region and did not include other regions in the Kingdom.

Conclusion and Recommendation

In summary, Saudi Arabia is still considered to be one of the endemic areas, and brucellosis should be considered as one of the diagnosis in any patient presenting non-specific symptoms. We recommend increasing public awareness about brucellosis in Saudi Arabia and its complications.

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Ethics Approval and Consent to Participate

The study was approved by the Research Center at King Fahad Medical City (IRB registration number H-01-R-012).

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