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Review Article

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Brucellosis in Children: A Single-Center Review of Clinical Manifestation and Antimicrobial Susceptibility

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ABSTRACT

Saudi Literature showed a shortage of recent data about pediatric brucellosis, particularly those concerned with the susceptibility of brucella isolates to antibiotics. This study aimed to describe the demographic, seasonal, and clinical and laboratory manifestations of pediatric brucellosis and to determine brucella isolates susceptibility to antibiotics. A retrospective study was conducted at Prince Sultan Military Medical Center (PSMMC), Riyadh, Saudi Arabia over ten years from 2007 to 2016. The study extracted data from the medical records of 81 children with brucellosis (65 males and 16 females). The data were collected by a well-developed data collection sheet. The sheet included socio-demographic data (age, sex, and nationality), as well as seasonal, clinical, and laboratory data. The collected data were analyzed using appropriate statistical methods. The mean age of the studied children were 8.2 ± 3.9 years, with 80.3% of them were males. Marked seasonal variation was detected all over the study years with the highest incidence was in the summer and autumn seasons. Fever and arthralgia were the most common presenting symptoms accounting for 83.9% and 48.1% of the studied cases, respectively. Anemia and leucopenia were found in about one-fourth of patients, while leukocytosis was found in only 8.7%. Liver dysfunction was also found in some patients with hyperbilirubinemia was the most predominant (98.5%). More than 70% of cases had an initial serology titer of 1/20480, and 8 patients (10.7%) have had a titer of > 1/640. Brucella isolates resistance was the highest to trimethoprim/sulfamethoxazole, with 27 isolates (33.3%) were resistant. For rifampicin, 8 of the tested 75 isolates (10.7%) were resistant. Continued efforts including surveillance and recording of full data of newly diagnosed cases should be warranted. Further pediatric studies are needed.

Key words: *Brucellosis, Children, Clinical presentation, Susceptibility, Saudi Arabia*

INTRODUCTION

Human brucellosis is an important zoonotic infectious disease caused by the bacterial genus *Brucella* [1-3]. There are four species pathogenic to humans: *Brucella melitensis*, found primarily in goats, sheep, and camels; *Brucella abortus* in cows; *Brucella suis* in pigs and *Brucella canis* in dogs [4, 5]. Currently, *Brucella melitensis* remains the principal cause of human brucellosis worldwide, including Saudi Arabia [6].

Brucellosis is an endemic disease in Saudi Arabia with a reported incidence of 18/100,000 population/year, as reported by the Saudi MOH in 2011, with a total seroprevalence rate was 15% among the adult population and 10% among children aged 14 years and younger [7]. Reports from endemic areas exhibited a high percentage of pediatric brucellosis accounting for up to half of the affected patients [5, 8-10]. The main source of childhood infection is through unpasteurized dairy items and traditional local foods including dairy products [8]. Clinical manifestations of childhood brucellosis are varied and range from minimal symptoms to extreme morbidity and

occasional fatality [11, 12]. Fever and arthritis are the most common clinical presentation, and brucellosis may be complicated by meningitis, endocarditis, osteomyelitis, and, less frequently pneumonitis and aortic involvement [13, 14].

Treatment of brucellosis required prolonged antibiotic therapy to achieving a cure, with combination therapy is recommended as a standard treatment regimen. The most common treatments are combined rifampicin and co-trimoxazole for young children < 8 years old or doxycycline and co-trimoxazole for children older than 8 years for a minimum of 6 weeks duration [14-17]. Antimicrobial drug resistance to the standard recommended empiric regimen, however, was reported in some studies [18-21]. Also, the authors of this report have observed an increasing number of *brucella* isolates resistant to rifampicin during their clinical practice. Treatment of such patients is challenging as an alternative drug regimen usually include ciprofloxacin or doxycycline. Ciprofloxacin is not approved by the FDA in children less than 18 years [22] as well as doxycycline can't be used in children younger than 8 years old [23]. Because of scarce Saudi reports about pediatric brucellosis, particularly those concerned with susceptibility of *brucella* isolates to antibiotics, this study aimed to describe the demographic, seasonal, and clinical and laboratory manifestations of pediatric brucellosis and to determine *brucella* isolates susceptibility to antibiotics in a retrospective sample of 81 cases of pediatric brucellosis at Prince Sultan Military Medical Center (PSMMC), Riyadh, Saudi Arabia over ten years from 2007 to 2016.

MATERIALS AND METHODS

A retrospective cohort of 81 confirmed cases of pediatric brucellosis at Prince Sultan Military Medical City (PSMMC) in Riyadh city, Saudi Arabia over ten years period from 2007 to 2016 was analyzed to examine their clinical manifestation and laboratory findings and to determine *brucella* isolates to antibiotics. PSMMC is a tertiary health care system with 1000 beds that serves a large population of Saudi soldiers and their extended families in Riyadh city, the capital of the Kingdom.

All children aged 14 years and younger diagnosed to have had brucellosis by documented blood culture during the study period were included in the study analysis. Information such as age, sex, nationality, date of onset, clinical presentation, laboratory finding including (CBC, liver function tests, CRP, ESR, *brucella* serology as well as sensitivity pattern of brucella isolates), treatment regimen, and its duration were collected. The diagnosis of brucellosis among the studied cases was made based on compatible clinical signs and symptoms in the presence of positive blood culture and/or serological tests of ≥ 1:160, using standard tube agglutination [24]. All studied patients were treated with combined antibiotic therapy. The study was approved by the PSMMC institutional research board (IRB), and ethical consideration was considered to ensure confidentiality and privacy of the collected data.

The statistical analysis was done using SPSS software, version 22.0, for Windows (SPSS, Inc., Chicago, IL). Data were statistically summarized by frequencies and percentages while continuous variables were presented as mean and standard deviation. Serology titer was compared by patients' age and sex using a chi-square test. The level of statistical significance was set at $P \leq 0.05$.

RESULTS AND DISCUSSION

The present retrospective study analyzed data from 81 Saudi children's cases with brucellosis at PSMMC during the period from 2007 to 2016. **Table 1** presented the distribution of the studied cases according to their age, sex, and seasonal diagnosis. The mean age of the studied children was 8.2 ± 3.8 years**,** and 45.7% (n= 37) of them were less than 8 years. The majority of reported cases were male (80.3) giving a male: female ratio of 4.1:1. Most of the cases were diagnosed in summer (44.5%) and autumn (29.6%) seasons; where 16% diagnosed in winter and 9.9% in the spring season.

Tables of the study

Table 1. Demographic and seasonal characteristics of the studied cases (n= 81)

Characteristic	n (%)
Age in years; mean ± SD	8.2 ± 3.9 years
Age in years	
< 8	37 (45.7)

≥ 8	44 (54.3)
Sex	
Male	65 (80.3)
Female	16 (19.7)
Seasons	
Spring	8 (9.9)
Summer	36 (44.5)
Autumn	24 (29.6)
Winter	13 (16.0)

Table 2. Clinical findings of the studied cases

Clinical findings	n (%)
Symptoms	
Fever	68 (83.9)
Joint pain or swelling	39 (48.1)
Chills	10 (12.3)
Poor appetite	12 (14.8)
Weight loss	11 (13.5)
Night sweating	10 (12.3)
Headache	8 (9.8)
Body aches	8 (9.8)
Abdominal pain	10 (12.3)
Cervical swelling	3 (3.7)
Vomiting	5 (6.1)
Cough	4 (4.9)
Testicular pain	1 (1.2)
Signs	
Arthritis	6 (7.4)
Hepatomegaly	8 (9.8)
Splenomegaly	7 (8.6)
Cervical Lymphadenopathy	3 (3.7)
Cardiac murmur	1 (1.2)
Abdominal swelling	1 (1.2)

Table 2 showed the distribution of the studied cases according to their clinical presentation. The most presenting symptom was fever (83.9%), followed by joint pain and swelling (48.1%). Other presenting symptoms were poor appetite (14.8%), weight loss (13.5%), chills, night sweating, and abdominal pain. Testicular pain was presented in only one patient (1.2%). Hepatomegaly and splenomegaly were detected in 9.8% and 8.7% of the studied cases, respectively. Acute painful arthritis, particularly in the knee, was found in 6 patients (7.4%). Cervical lymphadenopathy was detected in only 3 patients (3.7%) while cardiac murmur and abdominal swelling were found in only one patient.

Table 3. laboratory finding of the studied cases

	No. tested	N (%) abnormal
Leukocopenia (<5000 x lob/L)	80	20 (25.0)
Leukocytosis (>10000 x lob/L)	80	7 (8.7)
Anemia (Hb < 10gm/dl	79	8 (10.1)
Thrombocytopenia	81	9 (11.1)

High ESR (>40mm/h)	60	14 (23.3)
Bilirubin	70	69 (98.5)
ALT	67	13 (19.4)
AST	77	22 (28.6%)

Table 3 displayed the laboratory findings of the studied cases. Leukopenia (<5000 lob/L) was found in 25%, and leukocytosis (>10000 lob/L) was seen in only 7 patients (8.7%) of the test 80 patients, no one has exceeded 15000 lob/L. Anemia (Hb < 10 g/dL) was found in 8 (10.1%) of the tested 79 patients. The ESR was considered high (>40 mm/h) in 23.3% of the tested 60 patients. Thrombocytopenia was seen in 9 patients (11.1%) of the tested 81 patients. Elevated bilirubin was seen in 98.5% of the tested 70 patients (Bilirubin > 1 mg). Other elevated liver function tests were ALT (ALT > 55U/L) seen in 19.4% of the tested 67 patients, and AST (AST > 40 U/L) seen in 28.6% of the 77 patients tested. In this study, one patient had a positive peritoneal fluid culture.

Of the studied 81 cases there were three negative *brucella* serology tests. **Table 4** presented the mean *brucella* serology titer by the studied patients' age and sex. The mean brucella titer of the studied 81 patients was 1/30 ± 0.07. No statistically significant differences were detected by the patient's sex and age, although the titer was higher among the studied male patients and those aged less than 8 years. More than 70% of cases had an initial titer of 1/2048, and 8 patients (10.7%) have had a titer of > 1/640.

Table 4. Brucella serology titer among the studied cases by their age and test

	Brucella serology titre Mean ± SD	**P-value**
Total	1/30 ± 0.07	-
Sex		
Male (n= 65)	1/31 ± 0.07	
Female (n= 16)	1/25 ± 0.06	0.52
Age		
< 8 years (n= 37)	1/30 ± 0.08	
≥ 8 years (n= 44)	1/26 ± 0.06	0.19

Table 5. Brucella isolates resistance to antibiotics by the study years

Year	**Number of isolates tested**	**Trimethoprim Sulfamethoxazole**	**Rifampicin**	**Tetracycline**	**Gentamycin**	**Ciprofloxacin**
2007	6	3/6	0/6	0/5	0/5	0/5
2008	1	1/1	0/1	0/1	0/1	0/1
2009	18	13/18	0/18	0/18	0/18	0/18
2010	10	1/10	0/10	0/9	0/10	0/10
2011	4	3/4	0/4	0/4	0/4	0/4
2012	10	10/10	0/8	0/10	0/10	0/10
2013	6	0/6	0/5	0/5	0/6	0/6
2014	9	0/9	0/4	0/9	0/9	0/9
2015	6	0/6	0/4	0/6	0/6	0/6
2016	11	0/11	8/11	0/11	0/11	0/11
Total	**81**	**27/81**	**8/75**	**0/78**	**0/80**	**0/80**

Table 5 showed the *brucella* isolates resistance to antibiotics by year. Susceptibility tests performed showed that 27 isolates (33.3%) were resistant to trimethoprim/sulfamethoxazole (TMP/SMZ) and 8 isolates (10.7%) of the tested 75 isolates were resistant to rifampicin. No resistance to tetracycline, gentamycin, and ciprofloxacin was detected. Except for resistance to rifampicin, the study showed no resistance to other studied antibiotics in the recent year.

The various regimens of therapy used for the studied cases are shown in **Table 6**. A combination of rifampicin and doxycycline was used in 9 of the studied 41 patients. Rifampicin was also used in different combination with TMP/SMZ in 6 patients, and triple combination with TMP/SMZ and gentamycin in 7 patients. TMP/SMZ was combined with ciprofloxacin in 4 patients. Doxycycline was used in combination with ciprofloxacin in 4 patients and with streptomycin in another 4 patients. The mean duration of treatment of the studied patients was range 5.7 ± 0.7 weeks, and it was ranged from 4 to 6 weeks.

Table 6. Treatment regimen of the studied cases (n=41)

Treatment regimen	n (%)
Rifampicin + Doxycycline	9 (22.0)
Rifimpaicin + TMP/SMZ	6 (14.6)
Ciprofloxacin + TMP/SMZ	4 (9.8)
Rifamapicin + Gentamycin + doxycycline	2 (4.9)
Rifamapicin + Gentamycin + TMP/SMZ	7 (17.0)
Doxyclycine + Ciprofloxacin	4 (9.8)
Doxycycline + Streptomycin	4 (9.8)
Other combination	5 (12.2)

Brucellosis is considered one of the most significant health problems in Saudi Arabia where the disease is quite endemic, particularly in children. The present study analyzed retrospective data from a cohort of 81 children diagnosed with brucellosis over ten years to study their clinical and laboratory presentation and to determine the antibiotic susceptibility of *brucella* isolates. The disease was found more among male children (80.3%), with a male to female ratio of 4:1, and older children (54.3%). Previous Saudi reports also noticed a higher incidence among male children and older age groups [5, 8, 25]. In Greece, male predominance was noted for brucellosis; with a male to female ratio of 3:1 was noticed [26]. The male and older age predominance can be attributed to the occupation where they are mainly involved in animal husbandry and care [26, 27]. However, a female predominance was reported in a small Saudi report [28]. This report, however, was only including adult cases wherein certain Saudi areas, a female might be involved in animal care [29].

In this study, the highest incidence was reported in summer (44.5%) and autumn (29.6%) seasons. A similar high peak of human brucellosis from May to October was also reported in similar Saudi studies [5, 25, 29], and a report from Jordan [30]. The incidence of brucellosis in humans corresponds to grazing season with an increase in the consumption of unpasteurized milk, camel milk, resulting in a rise in the number of cases in these seasons.

The clinical presentation of brucellosis is very variable in the literature, partly because of the variable pathogenicity of different *brucella* strains. *Brucella abortus* usually causes milder disease, while *brucella melitensis* strain is usually associated with a high rate of bacteremia, and noticeable symptoms. In the present study, fever was the most common presenting symptom among the studied cases accounting for 89.3%. Similar observations have been reported in previous Saudi studies [5, 8]. Data on signs and symptoms of 1108 human brucellosis in the AL-Qassim region between 2010 and 2014, fever was the most common presenting symptom and accounting for 79.7% of the studied cases [25]. Arthralgia and joint pain and swelling were the second most common presenting symptoms in our study (48.1%) as in the previous one [25]. In our study, monoarthritis was more common than polyarthritis. The most commonly affected joints were the knee and hip. This finding, however, may create confusion in diagnosis in children and pyogenic arthritis may be suspected. Accordingly, in a community where brucellosis is quite common, fever and arthralgia in children should alert pediatricians for the possibility of brucellosis.

Hematological abnormalities are not uncommon in brucellosis. In the present study, about one-fourth of the tested cases had anemia (23.3%) and leukopenia (25%). Leukocytosis was seen less frequently in 8.7% of the tested cases. Similar findings were also found in a previous similar Saudi study [8]. Brucella infection commonly causes mild hematologic abnormalities [30] such as anemia and leukopenia. Thrombocytopenia is less common in our study. It has been seen in 11.1% and it was mild and no severe thrombocytopenia However, there has been a report of thrombocytopenic purpura associated with brucellosis [31], with high mortality due to hemorrhage into the central nervous system.

Of the studied 81 cases there were only three negative *brucella* serology tests. For other 78 positive serology test, the mean titer was 1/30 ± 1/0.07, and no statistically significant differences were detected by patient's sex and age, although the titer was higher among the studied male patients and those aged less than 8 years. In endemic areas, serologic testing is considered to be diagnostic when titers of more than 1/160 are present. A mean titer of 1/320 to 1/640 is also reported in these areas [32]. The sensitivity and specificity of a serologic test are generally very high [32]. In our study, more than 70% of cases had an initial titer of 1/2048, and 8 patients (10.7%) have had a titer of > 1/640.

For brucellosis, the World Health Organization (WHO) recommends six weeks of combination treatment with oral doxycycline plus rifampin for children older than 8 years of age [33]. Rifampicin and TMP/SMX for children below 8 years of age. In our study, the resistance of brucella isolates to antibiotics was the highest to trimethoprim/sulfamethoxazole (TMP/SMZ), before the year 2013, where 27 isolates (33.3%) were resistant. For rifampicin, 8 isolates (10.7%) of the tested 75 isolates were resistant and all these cases were reported in 2016. There was no resistance with ciprofloxacin, tetracycline, doxycycline, and streptomycin. Many studies have evaluated the use of fluoroquinolones [34] or macrolides [35] without demonstrating any in vivo superiority of these newer antibiotics. In vitro susceptibility to all of these agents remains very high. Monotherapy of brucellosis is associated with unacceptably high rates of clinical relapses and is not recommended [36]. Combination therapy with the doxycycline-aminoglycoside combination is the first choice with doxycycline- rifampin and doxycycline-cotrimoxazole should be the alternative regimens. In this study, similar combination treatment regimens were used. Neither case fatality nor long-term complications were reported among our studied 81 cases.

Although human brucellosis has been studied in Saudi Arabia among different regions, this research studied only children cases of brucellosis in terms of demographic, seasonal, clinical, laboratory data available at PSMMC from 2007 to 2016. Unlike other similar studies, this study has determined the susceptibility of brucella isolates to several antibiotics in common use. This study, however, is subjected to some limitations, being retrospective with missing data especially about long-term complications including risk or relapse could not be correctly managed. Also, the study data have emerged from a single center with a unique population, so the finding from our report might not reflect the whole spectrum of pediatric brucellosis all over the Kingdom.

In conclusion, this study showed marked seasonal variation in the incidence of pediatric brucellosis in Riyadh city during the period from 2007 to 2016, with the highest incidence was in the summer and autumn seasons. The incidence was more predominant among boys with a male to female ratio was 4:1. Fever and monoarthritis should warrant the pediatrician to a high index of suspicion of pediatric brucellosis. Combination therapy is the best for prompt treatment of human brucellosis with a duration period from 3 to 6 weeks. Surveillance and recording of new cases of brucellosis should be continued all over the year. Further studies are needed and to include data from multi-centers all over the Kingdom.

CONCLUSION

Pediatric brucellosis remains a public health problem in Saudi Arabia. Fever and arthralgia should alert pediatricians for the possibility of brucellosis. Continued efforts including surveillance and recording of full data of newly diagnosed cases should be warranted. Further pediatric studies are needed including data from different pediatric medical centers all over the Kingdom.

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