

# Human brucellosis in Northern Saudi Arabia

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## ABSTRACT

**Objectives:** Analysis of the clinical features, laboratory findings, treatment given and complications seen in brucellosis patients at the Northern Area Armed Forces Hospital, Hafr Al-Batin, Kingdom of Saudi Arabia.

**Methods:** We retrieved and reviewed the record charts of all patients from January 1995 to December 2001 with a clinical diagnosis of brucellosis whose brucella agglutination titre was 1:160 or greater from the Medical Records Department of Northern Area Armed Forces Hospital, Hafr Al-Batin. We extracted from the files the information on age, gender, occupation, history of raw milk or milk products ingestion, presenting symptoms and physical signs. We also noted the results of routine laboratory tests, treatment given, outcome of treatment and complications.

**Results:** One hundred and fifty-nine patients (males 101, females 58 with a ratio of 1.7:1) had a diagnostic label of brucellosis and a brucella titre of  $\geq 1:160$ . Thirty-three (20.8%) were  $\leq 12$ , 96 (60.3%) were 13-40 years old. Twenty-six (16.4%) were 14-60 years while 4 patients (2.5%) were  $\geq 60$  years. Fever ( $37.7^{\circ}\text{C}$ ) featured in 126 (79.2%) patients; joint pain in 112

(70.4%); while 77 (48.4%) had bone pain. We recorded the abdominal pain in 18 patients (11.3%) vomiting in 9 (5.7%) and anorexia in 6 (3.8%); splenomegaly in 6 (3.8%), hepatomegaly and lymphadenopathy in 2 (1.3%) patients. Brucella tube agglutination titres ranged from 1:160 to 1:5120. Thirty-eight (35.8%) patients had anemia (Hb  $< 12$  gms/dl); 12 patients (9.8%) had lymphocytosis (lymphocyte count  $> 1$  k/L). Ten patients (6.2%) had bacteremia. We used Rifampicin and doxycycline in 87 cases (54.7%), doxycycline and streptomycin in 33 (20.8%), and rifampicin and streptomycin in 20 (12.6%) for 6 weeks or longer (we used combinations including septrin in the remaining patients). We recorded relapse in 18 patients (11.3%). Pneumonia, epididymo-orchitis in 2 cases (1.3%) each, abortion, threatened abortion in one case each, complicated the disease in these patients.

**Conclusion:** Brucellosis is endemic in Northern Saudi Arabia as in other parts of the Kingdom. The clinical and laboratory features and response to therapy are also similar.

**Saudi Med J 2005; Vol. 26 (10): 1562-1566**

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The earliest report of human brucellosis in Saudi Arabia appeared in the literature nearly 2 decades ago.<sup>1</sup> Kambal et al<sup>2</sup> subsequently detailed the clinical features and laboratory diagnosis of the disease from the Riyadh area. Madkour et al<sup>3</sup> reviewed the clinical features in 140 Saudi Arab patients with brucellosis. Ninety of these patients had low back pain, arthritis, or both, at presentation; 32 had subacute hepatitis, abortion occurred in 6, epididymo-orchitis in 6, and endocarditis in 2. The study emphasized that brucellosis may be

misdiagnosed because it may mimic other illnesses. Fever and rheumatological findings were the dominant clinical findings in the report of Khan<sup>4</sup> of observations on 150 patients with brucellosis from the National Guard Hospital in Riyadh during a 2-year period in the 1980s. Fever, bone and joint complaints were the presenting features in a smaller series reported by Haddad and Smith<sup>5</sup> from the Security Forces Hospital also in Riyadh. Sixty percent of their patients with bone or joint complaints had an abnormal bone scan. Complete

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recovery occurred in these patients, but patients who discontinued their medication prematurely experienced relapse. Al-Zeftawi et al<sup>6</sup> investigated the epidemiology of brucellosis among abattoir workers from slaughterhouse sites in Dammam, Riyadh, Jeddah, Mecca, Qassim, Al-Hassa and Medina. The overall incidence of brucellosis among the workers was low at 1.8%. Positive titres were from veterinarians, butchers, laborers (all clinically symptomless), while administrative personnel, maintenance workers and drivers were negative. A more recent report on clinical and laboratory observation by Memish et al<sup>7</sup> in 160 patients that focused on brucellosis bacteremia underlined the fact that the spectrum of brucellosis can be from an asymptomatic illness to a severe bacteremic presentation. A large cross-sectional study from Southwest Saudi Arabia involved analysis of blood specimens from 1336 individuals from different areas of Asir region.<sup>8</sup> They recorded a significant titre in 58.7% of patients with fever compared with 0.9% of asymptomatic individuals. The report also stated that brucellosis was more prevalent in children under 12 years and that close contact with goats, sheep, cows and camel and consumption of raw milk were associated with contracting the disease. A 3-year survey in Abha General Hospital also in Asir Region by Malik<sup>9</sup> showed similar associations.

In this study, we report our retrospective study of human brucellosis in a secondary specialist hospital in the Northern Area of Saudi Arabia.

**Methods.** The record charts of all patients who presented between January 1995 and December 2001, with a clinical diagnosis of brucellosis and whose brucella agglutination titre by micro agglutination tube dilution test was 1:160 were reviewed. A diagnosis of brucellosis was made by clinicians and patient coded by medical records as brucellosis, if a patient had 2 or more of the following symptoms: fever, chills, headache, myalgia/arthralgia, fatigue, sweats, weight loss, weakness which are not otherwise explained plus a brucella tube agglutination titre greater than or equal to 1:160 or a positive blood culture for brucella. The age, gender, occupation, history of ingestion of raw milk or milk products, presenting symptoms and physical signs were extracted from the files. Also, extracted were the results of routine laboratory tests, treatment given and its duration and outcome as well as complications. The duration of follow-up recorded in the files ranged between 4-16 weeks. A relapse is recorded if a patient's symptoms, which had resolved after completion of treatment, relapsed with or without increase in agglutination titre or a previously negative blood culture becomes positive when symptoms relapsed.

***Brucella tube agglutination test procedure.*** The greatest dilution of patient's serum which caused agglutination of a known bacterial suspension prepared in the standard way was determined using SAS<sup>TM</sup> Febrile Antigens and Control Sera (SA Scientific, Inc. 4919 Golden Quail, San Antonio, Texas 78420 USA). The protocol of the suppliers was followed and titre of the serum is recorded as the last dilution that gives 50% (2+) agglutination. Blood cultures were manually applied in agar plates and processed in a growth indicator alarm on a Walkway Incubator.

***Diagnostic criteria.*** Any febrile illness with clinical suspicion of brucellosis (symptoms of chills, headache, myalgia/arthralgia, fatigue anorexia, sweats, weight loss, weakness) and brucella agglutination titre by tube agglutination dilution test 1:160. This is the criterion adopted by most of the reports cited in the introduction and falls into the Centers for Disease Control case classification probable.<sup>10</sup> The diagnosis is definite in the few cases who have a positive blood culture.

This study was conducted in July 2002 at the Northern Area Armed Forces Hospital, Hafr, Al-Batin, Kingdom of Saudi Arabia. It was approved by the Hospital's Research Committee.

**Results.** One hundred and eighty-two charts were screened, 23 (12.6%) were deleted from further analysis because the results of the brucella agglutination titers were not available, or there was duplication, leaving 159 (87.4%) patients case files for analysis. More cases were recorded in 1998 (69 [43.4%]) and 1999 (42 [26.4%]). There were fewer cases in 1995 (2 [1.3%]), 1996 (4 [2.5%]) and 1997 (8 [5%]), followed by an increase to 16 (10.1%) in 2000 and 18 (11.3%) cases in 2001. There were 101 (63.5%) males and 58 (36.5%) females with a male to female (M:F) ratio of 1.7:1. Thirty-three patients were  $\leq 12$  years. Ninety-six (60.3%) were between 13-40 years (M:F 2.4:1) as shown in **Table 1**. The presenting symptoms and signs are shown in **Table 2**. Fever, joint pains and bone aches were the most frequent symptoms. Gastrointestinal symptoms occurred in 39 (24.5%) patients. One (0.6%) patient presented with abdominal distension and one (0.6%) had acute appendicitis. However, there was paucity of physical signs (**Table 2**). Pneumonia and epididymo-orchitis, 2 cases each (1.3%), threatened abortion, complete abortion and appendicitis, one case each (0.6%) complicated the disease of these patients. The brucella tube agglutination titre results were 1:160 (22 patients: 13.8%); 1:320 (42 patients: 26.4%); 1:640 (37 patients: 23.3%). Twenty-four patients (15.1%) had a titre of 1:1280, while 23 patients (14.5%) had a titre of 1:2560 and 11 patients (6.9%) had a titre of 1:5120. Two patients with pneumonia had initial titres of 1:1280 and 1:2560. Blood culture was positive for brucella in

Table 1 - Age and gender distribution.

Age (yrs)	Females n (%)	Males n (%)	Total N (%)
12	18 (11.3)	15 (9.4)	33 (20.8)
13 – 30	17 (10.7)	43 (27)	60 (37.7)
31 – 40	11 (6.9)	25 (15.7)	36 (23.3)
41 – 50	1 (0.6)	12 (7.5)	13 (8.2)
51 – 60	9 (5.7)	4 (2.5)	13 (8.2)
> 60	2 (1.3)	2 (1.3)	4 (2.5)
<b>Total</b>	<b>58 (36.5)</b>	<b>101 (63.5)</b>	<b>159 (100)</b>

Table 2 - Presenting symptoms and signs in 159 patients.

Symptoms	n	(%)
Fever	126	(79.2)
Joint pain	112	(70.4)
Bone pain	77	(48.4)
Raw milk ingestion	43	(27)
Body ache	40	(25.2)
Headache	26	(16.4)
Sweating	20	(12.6)
Cough	19	(11.9)
Abdominal pain	18	(11.3)
Backache	16	(10.1)
Pharyngitis	13	(8.2)
Vomiting	9	(5.7)
Rigors	7	(4.4)
Anorexia	6	(3.8)
Weakness	6	(3.8)
Chills	5	(3.1)
Legs pain	4	(2.5)
Malaise	4	(2.5)
Fatigue	3	(1.9)
Diarrhea	2	(1.3)
Dizziness	2	(1.3)
Nausea		
Others: weight loss, epistaxis, Convulsion, lassitude, dyspnea	1 each	(0.63) each
Signs	n	(%)
Splenomegaly	6	(3.8)
Hepatomegaly	2	(1.3)
Lymphadenopathy	1	(0.6)
Jaundice	2	(1.3)

one of the 2 patients with pneumonia. Results of the complete blood count, erythrocyte sedimentation rate (ESR) and liver tests showed that anemia (hemoglobin [HB] <12 gm/dl) occurred in 38 (35.8%), lymphocytosis (lymphocytes > 1 k/L) in 20 (96.8%), and thrombocytopenia (platelets < 150 k/L) in 12 (9.8%) of those whose test results were in the chart. In those with anemia, HB was less than 10 gm/dl in 8 (7.5%) while total neutrophil count was less than 4k/ul in 11 (8.8%). The ESR was 20 mm/hr in 43 (60%) of 72 patients. Alanine transaminase was >50 u/L in 21 (23.3%) cases and aspartate transaminase was > 40 u/L in 61 (69.3%) cases. Forty-three patients (27%) had history of raw milk ingestion or ingestion of dairy products. However of 10 patients (6.3%) who had bacteremia, 4 (40%) had a history of raw milk ingestion. The initial titre for the 10 bacteremic patients ranged between 1:320-1:2560. The clinical presentation, laboratory findings and response to treatment were not different between the bacteremic and non-bacteremic patients. Rifampicin plus doxycycline in standard dosage was the treatment used in 87 (54.7%) cases; doxycycline and streptomycin for 3-4 weeks in 33 (20.8%); rifampicin and streptomycin in 20 (12.6%); and rifampicin plus co-trimoxazole in 19 patients (11.9%), doxycycline and co-trimoxazole in 4 (2.5%) as standard therapy in these patients. Duration of therapy was documented in 126 (79.2%) patients. It was equal to or less than 42 days in 62 (49.2%), 43-90 days in 56 (44.4%) and >90 days in 8 (6.4%) patients. There was documented evidence of relapse while on treatment in 18 (11.3%) patients on rifampicin and doxycycline combination. This was manifested by increase in brucella agglutination titre and recurrence of symptoms. Four (22.2%) of the relapsed patients gave history of raw milk ingestion with the first attack of the disease, but during relapse, there was no documentation of subsequent raw milk ingestion, or exposure to any risk factor for brucellosis. Two (11.1%) of the relapsed patients had bacteremia. The demographic data, presentation, and laboratory findings in patients who relapsed were similar to those who did not relapse. Pneumonia and epididymo-orchitis complicated the disease in 2 (1.3%) patients each and one (0.6%) patient had complete abortion while one (0.6%) patient had concomitant appendicitis. The patients with pneumonia had high titre of brucella agglutination, 1:1280, and 1:2560. Blood culture was positive for brucella in one of the 2 patients with pneumonia, while the patient with threatened abortion had a positive blood culture and a titre of 1:320.

**Discussion.** Our findings add to the body of information on the epidemiology and clinical

manifestation of brucellosis in Saudi Arabia with particular reference to the Northern region. Thirty-three (20.7%) patients were children (age 12 years). Brucellosis in children is particularly common in endemic areas.<sup>4</sup> Seasonal variation was observed in some reports.<sup>1,4,5</sup> Most cases in this study were diagnosed in 1998 during spring and early summer, when local people traditionally visit rural areas to enjoy spring and freshly expressed camel or goats milk.<sup>1,3,7</sup> The observed increase in cases in 1998 may be real or may be due to increased awareness of the disease by health care providers; better local laboratory diagnosis or combinations of these factors. The drop in the number of diagnosed cases in subsequent years could be due to improved awareness of the population of the causation and prevention of the disease. Forty-three patients (27%) gave a history of raw milk ingestion, while one (0.6%) had animal contact. These numbers probably could have been higher, if patients were asked direct questions about ingestion of raw milk or milk products. Fever and rheumatological complaints were the most frequently encountered symptoms, as in previous reports.<sup>1-5</sup> Thirty-one patients in this study had gastrointestinal symptoms. Gastrointestinal symptoms were also reported from the Asir region.<sup>9</sup> Al Aska<sup>11</sup> documented the variety of gastrointestinal manifestations of brucellosis in Saudi Arabia. Gastrointestinal symptoms may occur in 50-70% with brucellosis.<sup>12</sup> One patient presented with acute appendicitis: appendicitis in brucellosis is believed to be due to lymphoid hyperplasia.<sup>13</sup> Complications occurred in 7 (4.4%) patients: one patient had threatened abortion, one had complete abortion, 2 had epididymo-orchitis, 2 had pneumonia, and one had appendicitis. Although abortion has been reported in human brucellosis particularly in the first trimester of pregnancy, it is unclear whether it is more frequent than with other septicemic illnesses.<sup>12</sup> Genitourinary complications as epididymo-orchitis occurs in 5-9% of cases in some series.<sup>13</sup> Two (1.3%) of our patients had pulmonary brucellosis, a rarely reported presentation of brucellosis.<sup>8,14</sup> Apparently, it is acquired via inhalation of contaminated dust instead of ingestion,<sup>12</sup> though in one study, history of raw milk ingestion was obtained in 8 out of 9 (89%) patients with pulmonary brucellosis.<sup>14</sup> One of the 2 patients with pneumonia in this series had history of raw milk ingestion. The brucella agglutination titres in these patients with pulmonary brucellosis were 1:1280 and 1:2560. One of the 2 patients had concomitant pulmonary tuberculosis, with positive acid fast bacilli in his sputum and a calcific lung lesion. Other rare presentations of the disease not seen in our series are ocular,<sup>15</sup> spinal brucellosis,<sup>16</sup> neurobrucellosis,<sup>17</sup> peritonitis,<sup>18,19</sup> endocarditis,<sup>3,20</sup> and severe thrombocytopenia.<sup>21</sup> We also did not see

interstitial nephritis, glomerulonephritis or pyelonephritis.<sup>13</sup> Contrary to previous reports from different parts of Saudi Arabia,<sup>1,2,7</sup> *Brucella abortus* (*B. abortus*) accounted for 127 (78.9%) of positive serological samples in this series. In our laboratory, *B. abortus* reagent was used as the standard reagent to make the serological diagnosis for brucellosis. This may explain the higher proportion of *B. abortus* among our patients. However, because *B. melitensis* reagent was not used, we cannot make any firm conclusion of the species of brucella in this region. Most of our patients responded to a combination of rifampicin and doxycycline, on an outpatient basis or in the Primary Health Care (PHC) Clinic. However, 11.3% of patients on this combination experienced relapse. Initial monotherapy, as sometimes practiced in the PHC and private clinics should be discouraged as the practice would favor the development of resistance, relapse or both.

Brucellosis is an enzootic infection, endemic in domestic livestock of Saudi Arabia.<sup>22</sup> In the early 1980s importation of livestock with brucellosis was uncontrolled.<sup>22</sup> Animal husbandry was widespread and the habit of ingestion of unpasteurized milk and milk products or meat of infected animals was common. All these factors encouraged the endemicity of human brucellosis. The concerted efforts of concerned authorities that ensured that livestock was vaccinated (Royal Decree No. 5/6/17495 dated 25/12/1409) have been effective in controlling brucellosis. Also, the observance of the Zoonosanitary code for International Trade in Animals and animal products<sup>23</sup> will ensure that the disease will continue to decline in humans.

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