Acute brucellosis in Saudi families: Relationship between brucella serology and clinical symptoms

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Received 30 March 2004; received in revised form 30 June 2004; accepted 6 July 2004

Corresponding Editor: Richard Oberhelman, New Orleans, USA

KEYWORDS
Brucellosis; Screening; Family members; Symptoms; Saudi Arabia

Summary

Objective: To determine if screening family members of patients with acute brucellosis will enhance the detection rate of brucellosis and also to determine the relationship between symptoms and brucella serology.

Materials and methods: Family members from patients with acute brucellosis were interviewed and serologically screened. All seropositive family members were clinically and serologically followed for six months.

Results: Twenty-five acute brucellosis patients and their 178 family members were enrolled from January 2001 to February 2002. Of the 178 family members, 40 (23%) manifested various symptoms, 138 (77%) were asymptomatic, with an overall seroprevalence rate of 34 (19%). The rate of seropositivity among the symptomatic family members was 23 (58%) and for the asymptomatic was 11 (8%) (P < 0.001). The majority of the symptomatic family members (13 (57%)) had a high Brucella titer in comparison to one (9%) of the asymptomatic group (P < 0.001). Acute brucellosis was diagnosed and treated in 18 (78%) of the symptomatic seropositive family members and in four (36%), of the asymptomatic seropositive family members with an acute brucellosis prevalence rate of 22 (12%). All family members with acute infection recovered without sequelae; one patient relapsed (5%).

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Introduction

Brucellosis is endemic in Saudi Arabia and other parts of the world.1–7 Humans acquire the infection through the consumption of products of infected animals such as unpasteurized milk, cheese and raw meat.

In Saudi Arabia, the incidence of the disease is high, particularly in the Central Najed region, around the city of Riyadh, an area where part of the population has a nomadic heritage which perpetuates the ingestion of fresh camel, goat and sheep milk.7,8 In addition, direct contact with infected animals, their secretions or their carcasses could lead to infection through inhalation or accidental skin and mucous membrane penetration.9,10 Therefore, veterinarians, farmers, abattoir and laboratory workers are at increased risk of contracting the infection.10–12

Other than the possibility of transmission through blood transfusion and organ or bone marrow transplantation, brucellosis is not readily transmitted between human beings. Congenital brucellosis has been reported but it is rare.13–15 A few reports have shown an increased incidence of brucellosis among family members of an infected person, due mainly to exposure to the same source of infection rather than human-to-human transmission.12,16–20 Thus, any case diagnosed in such a family may be an indication of a population at risk.

In endemic areas such as Saudi Arabia, with a potentially high rate of exposure within the population, one may assume that for each reported case of brucellosis many infections go unrecognized. By active screening for brucellosis in such settings, more infected individuals will be identified earlier on in the course of the disease. Early identification with early initiation of therapy will reduce the incidence of complications and relapse.

In the authors’ previous report a seroprevalence rate of 13% among family members of acute brucellosis cases was found with the majority (74%) being symptomatic. But symptoms in the seronegative group were not evaluated. Therefore, it was not possible to conclude that screening should be restricted to the symptomatic group purely for cost effectiveness.21

The purpose of this study was to assess the significance of the presence of particular symptoms among family members in increasing the yield of screening, and to follow the course of symptomatic and asymptomatic seropositive family members to determine which would develop active disease.

Materials and methods

Study population

The study was performed in King Abdulaziz Medical City, a 750-bed tertiary care center located in Riyadh, Saudi Arabia, which cares for the Saudi Arabian National Guard soldiers, officers, employees and their dependents.

Throughout this segment of the Saudi Arabian population, many families maintain herds. The consumption of unpasteurized dairy products from camels, sheep and goats is common, even though routine vaccination against brucellosis is not administered to these animals. All the index cases were infected through ingestion of unpasteurized raw milk and there were no work-related infections.

Definitions

Index cases: these were National Guard employees or dependents diagnosed as having acute brucellosis during the period from January 2001 to February 2002 and who agreed to enroll in this study.

Acute brucellosis: the diagnosis of acute brucellosis was based on the Centers for Disease Control (CDC) definition which includes the presence of clinical signs and symptoms with evidence of Brucella spp invasion in positive culture or a four-fold or greater increase in titer of $\geq 1:80$ using the Standard Tube Agglutination Test (SAT) or a single high titer against Brucella spp of $\geq 1:160$.22

Family members: were defined as all individuals living in the same household as the index case and who agreed to be interviewed and tested.

Symptomatic seropositives: were defined as family members with Brucella antibody titer of $\geq 1:160$ and symptoms compatible with brucellosis.

Asymptomatic seropositives: were defined as family members with Brucella antibody titer $\geq 1:160$, without any clinical symptoms suggestive of brucellosis.

All family members of the index case that agreed to be enrolled in the study were interviewed for the presence of any symptoms during the three months prior to the diagnosis of the index case.
The initial interview was carried out by the first investigator (SA) using predesigned forms before taking a blood sample for serology. The symptoms sought were fever, night sweats, arthralgia, arthritis, headache, weight loss, muscle and bone pain. Throughout the study period the interviewer was blind to the serology result or any referral to the Infectious Disease Clinic. If a family member of an index case refused the interview or the screening blood test, the index case was not included in the study.

Family screening was carried out as part of the Infection Prevention and Control Department's activities in preparation for setting a policy to control brucellosis. The importance of family screening is due to the absence of ongoing animal disease eradication and the high prevalence of the disease in the Kingdom.

Patients who were not included in the study were not followed by the Infection Prevention and Control Department and were followed instead by the infectious disease specialist.

SAT was carried out using Brucella abortus and Brucella melitensis antigens (stained B. abortus SS14 and B. melitensis SS15 suspensions, Murex Diagnostic). A Brucella antibody titer of \( \geq 1:160 \) was considered positive. Another investigator (BA) reviewed all family members’ serology results, referring all positive results (SAT \( \geq 1:160 \)) to the Infectious Disease Clinic for further evaluation.

### Treatment and follow-up

The infectious diseases specialist prescribed treatment for the symptomatic and asymptomatic seropositive family members and decided whether additional testing was required. Adults were generally treated with doxycycline (100 mg twice daily) and rifampin (600–900 mg once daily) while children were treated with rifampin (10–20 mg/kg/day once daily) and trimethoprim-sulfamethoxazole (co-trimoxazole 10 mg/kg/day once daily) for a total of six weeks. Clinical follow-up and serology were carried out at two, four and six months respectively for all seropositive groups.

### Statistical analysis

The Statistical Package for Social Sciences (SPSS) and Microsoft Excel were used for statistical analysis. We expressed continuous variables as the mean ± S.D. (Standard Deviation) with median, using the \( X^2 \) test to compare proportions. For expected frequencies less than five in contingency tables, Fisher's Exact Test rather than the \( X^2 \) test was used. All statistical tests were two-tailed. All data were entered using Epi Info Version 6.02.

### Results

Acute brucellosis was diagnosed in 29 patients during the 13-month study period from January 2001 to February 2002. Of these, 25 index cases and their families agreed to enroll in this study. The families were subsequently interviewed and serologically screened. Four index cases and their families refused either the interview or the screening.

Of the total 178 family members, 84 (47%) were male and 94 (53%) female. The age distribution of family members was three months to 80 years with median age of 16.6 years. Forty (23%) manifested various types of symptoms and 138 (77%) were asymptomatic. Thirty-four (19%) were seropositive with Brucella antibody titer of \( \geq 1:160 \), and 144 (81%) were seronegative with Brucella titer of \( \leq 1:80 \) (Figure 1).

#### Symptomatic family members

Of the 40 symptomatic family members, 23 (58%) were seropositive and 17 (42%) were seronegative (Figure 1). The most common symptoms experienced were arthralgia 29 (73%), fever 12 (30%), malaise seven (18%), backache six (15%), headache five (12.5%) and arthritis two (5%). (Table 1).

Among the 23 (58%) symptomatic and seropositive family members, 12 (52%) were children \( \leq 14 \) years of age. The titers ranged from 1:160 to 1:20480 and 13 (57%) had a high titer of \( > 1:1280 \) (Table 2). Previous history of brucellosis was reported in eight (35%) and of these, one family member had a titer of 1:5120. The remaining seven all had a titer of 1:320 or lower.

Blood culture was obtained in 17 (74%) of the symptomatic seropositives and of these, eight (47%) were positive for B. melitensis (Table 2).

#### Asymptomatic family members

Among the 138 (77%) asymptomatic family members, only 11 (8%) were seropositive and 127 (92%) were seronegative (Figure 1). The majority, seven (64%), of the seropositives had a low titer of \( \leq 1:320 \), three (27%) had a titer of 1:1280 and only one (9%) had a titer of 1:5120 (Table 2). All four who had high titer \( \geq 1:1280 \) were children and all were considered as acute brucellosis and were treated. Six (55%) had previous history of brucellosis and all had a titer of \( \leq 1:320 \) (Table 2).
Follow-up

During the follow-up period, 18 (78%) of the symptomatic seropositives were considered as having acute brucellosis and were treated either initially or on follow-up if titers were rising (Table 2). In contrast, only four (36%) of the asymptomatic seropositives were considered as having acute brucellosis and received treatment ($P < 0.05$); three were treated initially and all were children with titer of $\geq 1:1280$. One, a 14-year-old, was treated six months later, secondary to rising titer and development of symptoms.

All patients were treated on an outpatient basis, except two pediatric patients who required admission secondary to severe arthritis, and one patient who required drainage and lavage of the hip joint. Among all 22 (12%) family members with acute

<table>
<thead>
<tr>
<th>Serostatus</th>
<th>Clinically Symptomatic</th>
<th>Clinically Asymptomatic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Positive $n = 34$ (19%)</td>
<td>23 (58)</td>
<td>11 (8)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Serum Negative $n = 144$ (81%)</td>
<td>17 (42)</td>
<td>127 (92)</td>
<td></td>
</tr>
</tbody>
</table>

* Some patients had more than one symptom.
brucellosis only one (5%) relapsed five months after treatment and none developed significant side effects. All untreated seropositive patients remained well, with either stable or decreasing titers during the six months of follow-up. All symptomatic and asymptomatic seronegative family members were referred to the primary physician for further diagnosis and follow-up.

Discussion

In this study, it was found that the seroprevalence of brucellosis in family members of acute brucellosis cases is 19%. This is lower than has been reported in Peru (50.9%) and more than has been reported in Israel (9%).17,19 This variation in the seroprevalence rate among household contacts could be attributed to the differences in predisposing factors such as exposure to the same risk factor and the degree of this exposure. In a previous study a seroprevalence rate of 13% was reported and it was demonstrated that family members who gave a history of raw milk ingestion and living in a large household of more than five members were at greater risk of being seropositive.21

Such studies prove that serological screening of family members will detect additional cases of brucellosis.12,16–20,22 Due to the limitations of the SAT tests in its ability to differentiate between acute, chronic or past infection, diagnosis of acute brucellosis among family members in this study was dependent on the evaluation of the clinical symptoms, a SAT titer of >1:160 and the follow-up titers.

In this report, the evaluation of 25 index cases uncovered 34 (19%) seropositive family members of whom the majority, 22 (65%), had active infection with an acute brucellosis prevalence of 12%. This means that for each diagnosed case, there is almost one unidentified acute brucellosis case. The combination of clinical symptoms, serology and follow-up of family members will therefore identify acute brucellosis. In this study, if only the seroprevalence rate of 19% is taken into account the number of acute brucellosis cases would be overestimated.

Early and prompt therapy has been shown to provide rapid recovery without complications, despite brucellosis being known for its complications and chronicity.5,23–28 Around 10% of affected patients have one or more systemic complication, which is usually difficult to manage and frequently ends in chronic disability.26,27,29 In addition, chronic brucellosis has been reported in 10–20% of patients.23,28

The outcome in the treated family members reported here was excellent — all recovered rapidly without complication and only one patient (5%) relapsed. Therefore, the benefit of a screening program is early detection and early treatment resulting in fewer complications. Additionally, family screening in Saudi Arabia is important due to the absence of an ongoing animal disease eradication campaign.7,8 The testing and vaccination of imported domestic animals is carried out, however, there is no campaign to target the already infected local domestic animals within the Kingdom which means there is continuous exposure to infected animals and their secretions.

This is thought to be the first study to compare the seropositivity of symptomatic and asymptomatic family members from families with acute brucellosis cases. Most studies, including the authors’ previous report, have looked into the seroprevalence rate but have not evaluated the clinical

<table>
<thead>
<tr>
<th>Table 2</th>
<th>The relationship between the clinical symptoms, SAT titers and treatment in seropositive family members.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seropositives</td>
</tr>
<tr>
<td></td>
<td>Symptomatic 23 (58%)</td>
</tr>
<tr>
<td>SAT titer</td>
<td></td>
</tr>
<tr>
<td>≤1280</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>&gt;1280</td>
<td>13 (93%)</td>
</tr>
<tr>
<td>Previous history of brucellosis</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>8 (57%)</td>
</tr>
<tr>
<td>Negative</td>
<td>15 (75%)</td>
</tr>
<tr>
<td>Blood culture</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>8 (100%)</td>
</tr>
<tr>
<td>Negative</td>
<td>9 (69%)</td>
</tr>
<tr>
<td>Acute brucellosis diagnosed</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>18 (82%)</td>
</tr>
<tr>
<td>No</td>
<td>5 (42%)</td>
</tr>
</tbody>
</table>

<sup>*P</sup>-value calculated using Fisher’s Exact Test; SAT: Standard tube agglutination test.
status of the screened individuals.\textsuperscript{21,29} The rate of seropositivity among symptomatic family members was very high at 58%. This is in contrast to 8% in asymptomatic contacts (\(P < 0.001\)). This may imply that the cost effectiveness of screening all family members regardless of symptoms may be questionable, especially in developing countries with limited resources. Screening must be considered in light of the medical facilities available, the incidence of the disease, the demographic characteristic of a given population and the screening test used.

Based on the results here, it is recommended that screening family members of an acute brucellosis patient can be limited to the symptomatic members only. However, it is thought that children under 14 years of age should be screened regardless of their symptoms. In this cohort of asymptomatic seropositives, six (55%) were children and four of them were thought to have acute brucellosis and require treatment upon evaluation by the infectious diseases specialist. This could indicate that their symptoms may have been underestimated when initially interviewed.

Human brucellosis is a multisystem disease that is characterized by a multitude of somatic complaints, including arthritis, arthralgia, fever, night sweats, anorexia, fatigue, malaise and weight loss.\textsuperscript{2,3,6} In this study it was found that fever and arthralgia are more likely to be associated with seropositivity. Previous studies have shown these symptoms are the most common and prevalent symptoms in brucellosis.\textsuperscript{2,3} A screening program guided by a questionnaire regarding specific symptomatology such as fever and arthralgia is an excellent method for the early detection of active brucellosis cases and thus early institution of therapy with satisfactory outcome.

In conclusion, screening the family members of acute brucellosis cases will detect more acute infections. Symptomatic family members are more likely to be seropositive in comparison to the asymptomatics. Based on this, screening the family members of acute brucellosis in an endemic area is strongly recommended to enhance the detection rate, initiate early treatment and reduce complications. Where resources are limited, the screening of family members could be limited to the symptomatic and to children.

\textit{Conflict of interest:} No conflict of interest to declare.

References


