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Importance of screening household members of acute brucellosis cases in endemic areas

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SUMMARY

Isolated reports of brucellosis among family members have been documented. The aim of this study is to determine if active serological screening of the households' members of acute brucellosis cases will detect additional unrecognized cases. From May 2000 to October 2001, patients with acute brucellosis were enrolled and their household members were serologically screened for brucellosis using the Standard Agglutination Test (SAT). Fifty-five index cases with acute brucellosis and 404 household members were enrolled. The majority of index cases (48%) were young adults, and 79% were illiterate. Ownership of animals and ingestion of unpasteurized raw milk were reported by 45 and 75% of the index cases respectively. Of the 55 families screened, 23 (42%) had two family members or more with serological evidence of brucellosis and 32 (58%) had only the index case. Households of $\geqslant 5$ members and a history of raw-milk ingestion by family members were risk factors associated with the seropositives ($P < 0{\cdot}05$). Of the 404 household members screened, 53 (13%) were seropositive; of these 39 (74%) were symptomatic, and 9 (35%) had brucella bacteraemia. Symptomatic seropositives tended to have bacteraemia and higher brucella antibody titres compared to asymptomatic seropositives ($P \leqslant 0{\cdot}05$). Screening family members of an index case of acute brucellosis will detect additional cases.

INTRODUCTION

Brucellosis is a major health problem in Saudi Arabia, ranking in the top three communicable diseases reported among the Saudi Arabian National Guard population, and by the Ministry of Health over the past 10 years [1, 2]. National statistics from the Saudi Arabian Ministry of Health showed that the incidence of brucellosis peaked in 1990 at 72 cases/100 000 persons per year and has been steady between 32 and 38 cases/100 000 persons per year since 1996 [1]. The control of the disease in domestic animals has been unsuccessful and the consumption of unpasteurized raw milk and to a lesser extent, contact with the infected animals are the main sources of infection in our population [3, 4]. The consumption of unpasteurized raw milk, mainly from camels and sheep, is a traditional practice in the Kingdom of Saudi Arabia,

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especially among Bedouins [5]. This represents a large segment of the population at risk of getting the disease. Other modes of transmission, although rare, included vertical transmission from mother to child, transmission through breast milk, eating uncooked meat, sexual, and transmission to laboratory workers through inhalation [6–9]. Transmission of the disease among different members of the same family has been reported [10–13]. The mode of transmission is assumed to be due to sharing the same risk factors of drinking and eating unpasteurized dairy products. Brucellosis presents a difficult diagnostic challenge due to its chronic course and variable clinical manifestation [14, 15]. Considering the difficulty in the diagnosis, and the potentially high rate of exposure within our population, one may assume that for each diagnosed case of brucellosis, there are many from the same family practising the same drinking and eating habits that may remain unrecognized [16]. They may even present late in the course of the disease with a complicated disease involving critical organs like the central nervous system, heart and skeletal system [17, 18]. The aim of this study was to determine whether serological screening of the family members of an index case would uncover additional unrecognized cases of brucellosis in an endemic area such as Saudi Arabia. This would enhance the detection rate, provide early diagnosis and allow for early treatment. This strategy would be cost-effective since early diagnosis and treatment will reduce long-term complication and dissemination of the disease to other organs, with a subsequent reduction in morbidity and hospitalization. Furthermore, the importance of family screening lies behind the absence of ongoing animal disease eradication campaigns in the kingdom. A major national campaign was mobilized by the Health and Agriculture ministries, which included the testing and vaccination of all imported animals, improving the health education of the general public, and the vaccination of $>20\,000\,000$ domestic animals within the kingdom over a 4-year period. However, this campaign ceased in 1994 and although currently testing and vaccination of imported domestic animals is carried out, there is no campaign to target local domestic animals within the Kingdom of Saudi Arabia [1].

MATERIALS AND METHODS

A prospective epidemiological survey was performed at King Abdulaziz Medical City–Riyadh (KAMCR), a 750-bed tertiary care centre in Riyadh, Saudi Arabia serving the National Guard soldiers and their families. The population of the Saudi Arabian National Guard can be considered as being in transition from Bedouin to an urban lifestyle, where many of these families continue to have close contact with livestock through frequent visits to farms and the desert where the herds of sheep, goats and camels are reared. Many of these families own livestock for their domestic use and they are the main source of their dairy products, and the consumption of unpasteurized raw milk is very common. In fact, many believe that boiling removes the 'goodness' from the milk.

Definitions

Index cases. Patients (adult or child) presented to KAMCR during the period from May 2000 to October 2001 with the diagnosis of acute brucellosis and who agreed to enrol in the survey.

Acute brucellosis. The diagnosis of acute brucellosis was based on the Centre for Diseases Control (CDC) definition, which includes the following:

Clinical description. An illness characterized by acute or insidious onset of fever, night sweats, undue fatigue, anorexia, weight loss, headache, and arthralgia.

Laboratory criteria for diagnosis. Isolation of *Brucella* sp. from a clinical specimen, or a fourfold or greater rise in *Brucella* agglutination titres between acute-phase and convalescent-phase serum specimens obtained $\geqslant 2$ weeks apart and studied at the same laboratory, or demonstration by immunofluorescence of *Brucella* sp. in a clinical specimen.

A probable case. A clinically compatible case that is epidemiologically linked to a confirmed case or that has supportive serology (i.e. *Brucella* agglutination titre of $\geqslant 160$ in one or more serum specimens obtained after onset of symptoms).

Confirmed. A clinically compatible case that is laboratory confirmed [19].

Household members. Any family member living in the same household of the index case; consuming the same foods, drinks, and practising similar occupational and recreational habits. Household members includes adults and children.

Seropositive household members. Any household members of an index case with Standard Agglutination Test (SAT) titres of $\geqslant 1:160$.

Seronegative household members. Any household members of an index case with SAT titres of $\leqslant 1:80$.

Index cases that agreed to be enrolled in the survey were interviewed. Interviews were carried out by two public-health nurses using a pre-designed form. The questions included demographic data of the index case, e.g. age, sex and level of education, the number of household members. The questionnaire also included epidemiological data concerning the whole family, e.g. owning animals, relatives owning animals, family visiting a farm and the frequency of such visits. History of drinking unpasteurized raw milk or handling animals by the index case or any family members, were also recorded. There were no details collected on specific handling practices like milking, herding or assisting with the birth of different species of animals. The questionnaire also included any previous history of brucellosis of the index case, or any family member, and whether treatment was received or not. The enrolment of the family members was carried out by the two public-health nurses. The family members were encouraged by the fact that the disease can exist with mild or no symptoms and early diagnosis and treatment would be beneficial. Only index cases who brought all family members for testing are included in the final analysis. All household members were asked to submit a blood sample for brucella serology testing using SAT. Titres of *Brucella* agglutinating antibodies were measured by a microtitre agglutination procedure using *Brucella abortus* and *Brucella melitensis* antigens (stained *B. abortus* SS14 and *B. melitensis* SS15 suspensions containing approximately 10^{10} organisms/ml; Wellcome Diagnosis, Dartford, UK); all sera were routinely diluted from 1:80 to 1:20480 to overcome prozone phenomenon. Each batch of tests included a positive 1:1280 control and a negative saline control. A definite agglutination of the suspension was read as a positive reaction. If prozone phenomenon was encountered, the higher dilution agglutination was recorded [20].

The SAT was performed on all family members within 1–3 weeks of the identification of the index case. Brucella antibody titre of $\geqslant$1:160 was considered positive and the household members were referred to an infectious diseases clinic for further evaluation. Blood samples were not cultured for *Brucella* sp. routinely, however, some index cases and some seropositive household contacts were cultured by infectious diseases specialists, based on their mode of practice. Some attending preferred to obtain blood culture from each patient, some depended on their clinical judgement and the likelihood of bacteraemia. Treatment of the index case and the seropositive household contact(s) were left to the discretion of the infectious diseases specialists. Adults were generally treated with 100 mg doxycycline twice daily and 600 mg rifampicin p.o. once daily, while children were treated with 20 mg/kg rifampicin once daily and 10 mg/kg trimethoprim–sulphamethoxazole once daily for a total of 6 weeks.

Statistical analysis

The data was entered in the computer using Version 6.02 of the Epi-Info statistical software. Frequency tables and cross-tabulation were produced. Student's test and χ^2 test were used for continuous and categorical data respectively.

RESULTS

Index cases

Of the 369 reported cases of brucellosis in the National Guard-dependent clinics in the Riyadh area, 131 (36%) presented to KAMCR and fulfilled the criteria for enrolment in the study. Seventy-six (58%) were excluded for various reasons, such as failure to contact the index case, refusal of the family members to be tested, and loss of follow-up of either index cases or of the positive household contacts. The remaining 55 (42%) index cases and their families were enrolled in the study and were followed up for 6 months. The age distribution was 2–67 years with a mean age of 27·1 years (S.D. = 17 years), children $\leqslant$13 years of age accounted for 14 (26%) of the cases, young adults between 14 and 40 years represent 26 (48%), and patients over 41 years represent 15 (27%) of the cases. There was a similar distribution among sexes with 31 (56%) males and 24 (44%) females. The majority of index cases, totalling 43 (79%) were either illiterate or had only primary-school education, 10 (18%) had finished high school and only 1 (2%) index case was a college graduate (Table 1).

A previous history of brucellosis was reported by 10 (18%) of the index cases; 9 (90%) were treated. Time of previous brucellosis was within the last year in 5 (50%) cases, 2–5 years in 4 (40%) cases and more than 5 years in 1 (10%) case. All index cases had a brucella SAT performed with a titre of 1:160 to 1:1280 observed in 14 (25%) cases; a titre of 1:2560 to 1:5120 in 17 (31%) cases; and a very high titre of 1:10240 to 1:20480 in 24 (44%) cases. Blood culture was obtained in 41 (75%) cases, of these 19 (46%)

Table 1. *Demographic and clinical characteristics of the index cases of acute brucellosis*

Variable	Frequency	%
1. Age (years)		
2–13	14	26
14–40	26	48
⩾41	15	27
2. Sex		
Male	31	56
Female	24	44
3. Education		
Illiterate	19	35
Primary school	24	44
Finished high school	10	18
College	1	2
4. Previous history of brucellosis		
Yes	10	18
No	45	82
5. Blood culture		
Positive	19	35
Negative	22	40
Not done	14	25
6. SAT titres		
1:320 to 1:1280	14	25
1:2560 to 1:5120	17	31
1:10 240 and ⩾1:20 480	24	44

Table 2. *Epidemiological and clinical data of the 55 households evaluated*

Variable	Frequency	%
1. Own animals	25	45
Sheep	25	100
Goat	19	76
Camels	16	64
Cows	2	8
2. Relative(s) own animal(s)	40	73
3. Dependent on farm as a source of dairy products	25	45
4. Frequently visited a farm	41	75
5. Raw-milk ingestion by index case	41	75
Goat	22	54
Sheep	15	37
Camels	25	61
Cows	2	5
6. Family members ingested raw milk	39	71
7. Handle animals and their products	23	42
8. Household with only the index case affected	32	58
9. Household with ⩾2 members identified as seropositive	23	42
2 members	7	13
3 members	10	18
⩾4 members	6	11

were positive for *B. melitensis* and 22 (54%) were negative (Table 1).

Epidemiological risk factors

The majority of the households, 25 (45%) owned animals; all of which had sheep, 19 (76%) had goats, 16 (64%) had camels and only 2 (8%) households had cows (Table 2). Ownership of animals by relative(s) was reported by 40 (73%) households and were mainly goats, sheep and camels. Frequent visits to a family farm and dependency on a farm as the main supply of their dairy products was reported by 41 (75%) and 25 (45%) households respectively. Their last visit to a family farm ranged from as recent as 1 week to as long ago as 20 weeks with a mean of 6·02 weeks (S.D. = 4·8 weeks). Raw-milk ingestion was reported by 41 (75%) of the index cases, mainly from goats in 22 (54%), sheep in 15 (37%), camels in 25 (61%) and cows in 2 (5%) (Table 2). The majority of index cases, 39 (71%), reported that other family members ingested raw milk; of these 28 (72%) reported that all their household members ingested raw milk at least once. Handling of raw meat, animals and their excreta were reported by 23 (42%) (Table 2). Among all households, 23 (42%) had ⩾2 members identified as being seropositive for brucellosis. Of these, 7 (13%) families had 2 members seropositive; 10 (18%) had 3 members seropositive and 6 (11%) families had between 4 and 7 members seropositive (Table 2).

Table 3 compares the households with only the index case infected to the households with two or more seropositive members (including the index case). There were no major epidemiological differences between these families, however, family size of more than five persons and history of raw-milk ingestion by family members were the two significant risk factors associated with identification of seropositive household members (Table 3) ($P < 0{\cdot}05$).

Household members

Of the 55 index cases evaluated, there were 404 household members contacted and then tested using SAT. The number for each family ranged from 1 to 18 people of normal distribution with a mean of 8 (S.D. 3·0). Of all the household members (not including the index case), serological evidence of infection with *Brucella* sp. was identified in 53 (13%). Their SAT titres ranged from 1:320 to ⩾1:20 480. Blood

Table 3. *Comparison between families with two or more seropositive household members* (*23*) *to families with seronegative household members* (*32*)

	Families with seropositive household members (23)		Families with seronegative household members (32)		
Variable	*n*	(%)	*n*	(%)	*P* value
1. Family own animals	12	(52)	13	(41)	0·39
2. Relatives own animals	16	(70)	24	(75)	0·66
3. Visit a farm frequently	20	(87)	21	(72)	0·20
4. Handle animal and other excreta	12	(52)	11	(36)	0·22
5. Depend on farm for their dairy product	12	(52)	13	(41)	0·39
6. Raw milk ingested by family member	21	(91)	18	(56)	0·017
7. Received raw dairy product as a gift	17	(74)	22	(69)	0·6
8. Number of household members of $\geqslant 5$	22	(96)	20	(63)	0·004

culture was obtained in 26 (50%) of the seropositive household members, of these 9 (35%) were positive. Thirty-nine (74%) of the seropositive members were symptomatic, which included all patients with brucella bacteraemia (Fig.). Symptomatic seropositive household contacts tended to have high brucella antibody titres of $\geqslant 1:2560$ compared to asymptomatic seropositives (67 *vs.* 21%) ($P \leqslant 0{\cdot}05$). The majority of asymptomatic households (64%) had a previous history of brucellosis and all had low titres while only 13% of symptomatics had a previous history of brucellosis. All symptomatic patients were treated, upon evaluation by the infectious diseases specialist in paediatric and adult infectious diseases clinics. Of the asymptomatic seropositive group, three were treated initially because of high titres, and two were treated 6 months later when symptoms developed and titre increased, the remaining nine were not treated, and follow-up titre at 6 months continued to be low (Fig.).

DISCUSSION

In a brucellosis endemic area, identifying the population at risk is important to detect unrecognized cases. Different epidemiological and diagnostic strategies have been used to identify cases and have led to a higher incidence of the disease than has been reported [21, 22]. In Ireland, for example, the number of reported cases increased with the instigation of the eradication programme that subsequently led to an increased public awareness and improved diagnostic services [21]. In Israel, active screening of one Bedouin town, located in the Negev region of Israel, increased the detection rate and actually doubled the incidence of brucellosis in that region [22]. An increased prevalence of brucellosis is expected to be seen among family members of an acute case of brucellosis since they share similar culinary habits [12, 23]. Gotuzzo et al. [13] retrospectively evaluated 39 families and 232 members and observed a high rate (50·9%) of symptomatic infection among the family members. Several risk factors for disease acquisition were identified in this report and included: age greater than 10 years, families with five or less members and exposure to a common source of infection. They also observed that treatment in the early stages of the disease had a better outcome than when delayed [13]. In 1994, Wallach et al. [12] described an outbreak of *B. melitensis* in a family where 9 out of 14 members became ill with microbiological and serological evidence of brucella infection. Other similar outbreaks within a family have also been reported [10, 11].

In our report we were able to detect additional cases of brucellosis through prospectively screening all family members of an index case. Families with household size numbering more than five members and with a history of raw-milk ingestion were at a higher risk for acquiring brucellosis. This was contrary to what has been reported by Gottuzo et al. [13]. Our patient population differed from that of Gottuzo's, where we had larger families with an average of eight members per family. In addition, our population is of low socioeconomic status and educational level where consumption of unpasteurized raw milk and food sharing is common practice. Raw-milk ingestion was considered the likely source of infection among our family members, which is in agreement with previous reports [3, 5, 24]. Seropositive household members were more likely to be symptomatic (74%), however

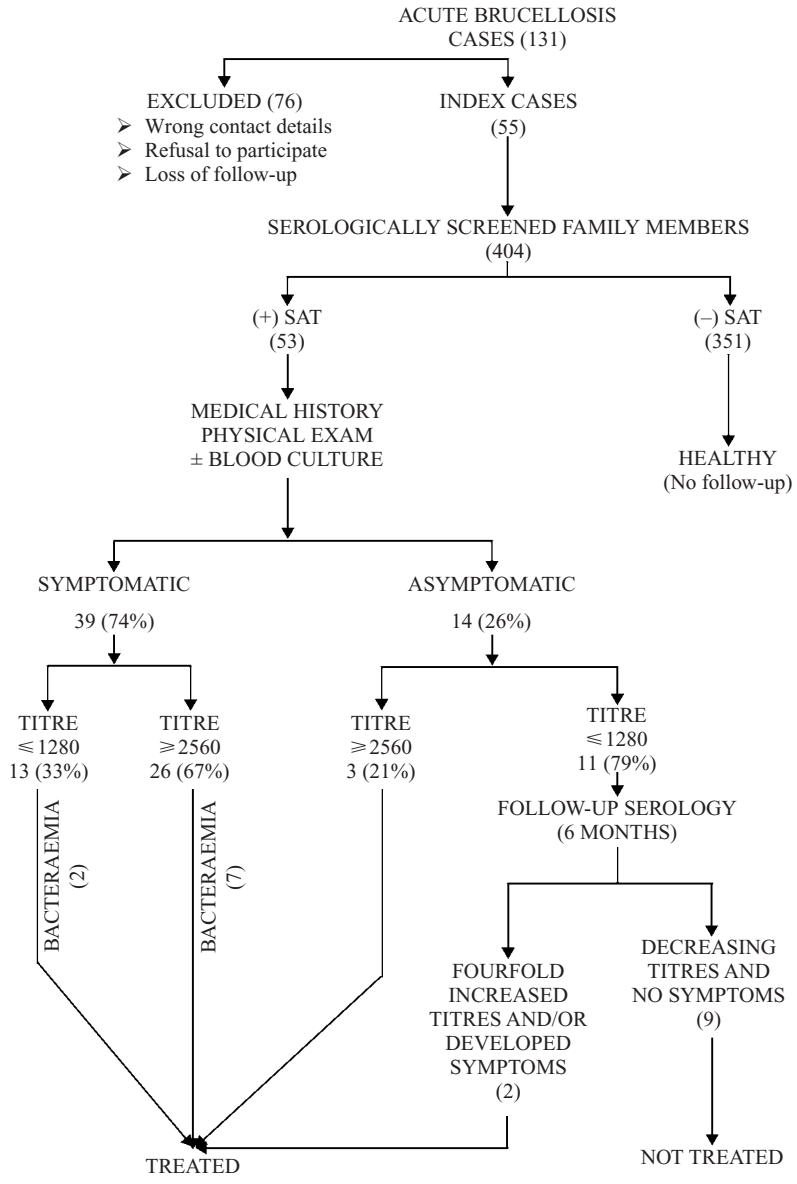

Fig. Screening procedures and outcome of index cases and their family members.

we cannot consider presence of symptoms as a risk factor from this study since symptoms were not evaluated in the seronegative group. In our institution, the majority of symptomatic patients were treated regardless of the height of the titre. Asymptomatic patients with positive titre in an endemic area may represent patients with previous brucellosis infection, subclinical infections, or infection in the early stages. Management of this group is challenging, and follow-up of the patients for development of symptoms or evidence of a fourfold increase in titres is recommended before the initiation of treatment [25]. To our knowledge, there is no study that has determined the efficacy of treating asymptomatic seropositive patients or the percentage that eventually will develop symptoms. In addition, little is known regarding the maintenance of immunity to re-infection by continued exposure. In this report, we followed 14 asymptomatic seropositive patients, of whom 9 (64%) continued to be asymptomatic with decreasing or stable titres, 2 (14%) developed symptoms and had a fourfold increase in titres during 6 months of follow-up, and 3 (21%) were treated initially, and this was influenced by the high titre of $\geqslant$2560. We believe this treatment is not justified since the patients do not fulfil the case definition criteria [19].

In our study, we uncovered at least one unidentified case of brucellosis for every diagnosed case, and screening of household members of acute brucellosis cases seemed reasonable because, first, family members are usually exposed to the same source of infection as the index case. Secondly, many of the seropositive household members identified in this study were asymptomatic or had mild symptoms that did not require medical advice and this would not have been discovered without screening. Furthermore, 9 (35%) of the seropositive household members had brucella bacteraemia and all had mild symptoms that did not require medical attention and were identified through screening.

Based on the above, we advise the screening of household members of acute brucellosis cases in endemic areas. The major benefits include early diagnosis and treatment, which is likely to decrease the rate of complication and relapse. In areas where resources are limited, one may consider selective screening of households at highest risk of acquiring the disease rather than screening all family members of an index case. In this way we identified selective screening of larger families and those with a history of raw-milk ingestion to be justifiable. Additionally, the importance of family screening lies behind the absence of an ongoing animal disease eradication campaign in the kingdom. Testing and vaccination of imported domestic animals is carried out. However, there is no campaign to target the infected local domestic animals within the kingdom, which we believed should be carried out along with education of the general public. Health education is initiated in our hospital through this programme where our public-health nurses visited homes, distributed brochures about the disease, and explained the link to raw-milk ingestion.

In conclusion, our screening programme demonstrated that for each case of brucellosis detected, there will be at least one additional case present among the family members. This accurately estimates the true prevalence of brucellosis. Screening of household members is justified in an endemic area for early diagnosis and treatment.

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