A study of 235 cases of human brucellosis in Sana'a, Republic of Yemen

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دراسة لمئتين وخمس وثلاثين حالة من داء البروسيلات في الإنسان في صنعاء بجمهورية اليمن

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خلاصة: أُجريت دراسة للخصائص السريرية لداء البروسيلات لدى 235 من المصابين الكبار والصغار بهذا المرض في مدينة صنعاء. ولقد شملت الدراسة جميع المصابين بداء البروسيلات، المحالين إلى المختبر الصحي المركزي من المستشفيات الرئيسية في صنعاء، خلال العامين 1992-1993. ولقد أُخذت قصة المرض من كل مريض، وأُجري له فحص سريري، فضلاً عن فحوص مختبرية عامة وأخرى لداء البروسيلات. وتبيَّن أن الصورة السريرية العامة لداء البروسيلات، حسبما أسفرت عنه هذه الدراسة، شديدة الشبه بتلك التي سجلها باحثون آخرون في هذه المنطقة الجغرافية. إن الوعي بالملامح المرضية، وإدراك أن داء البروسيلات ينبغي أن يؤخذ في الاعتبار ضمن التشخيص التفريقي في المرضى المصابين بالحمى مع تضخُّم الكبد والطحال والعُقد اللمفية، سوف يؤدي إلى ارتفاع مَنْسب الاشتباه في الإصابة بهذا المرض.

ABSTRACT We studied the clinical characteristics of brucellosis among all patients with brucellosis referred to the Central Health Laboratory from the main hospitals in Sana'a during a 2-year period (1992–93) (235 adults and children). A history was taken from each patient and clinical examination, general laboratory tests and brucellosis laboratory tests carried out. The overall clinical picture of brucellosis in this study is very similar to that reported by other workers in this geographical area. Awareness of the presenting features and the realization that brucellosis should be part of the differential diagnosis of febrile patients with enlarged liver, spleen and lymph nodes will lead to an increasing index of suspicion for this disease.

Etude de 235 cas de brucellose humaine à Sanaa (République du Yémen)

RESUME Nous avons étudié les caractéristiques cliniques de la brucellose chez tous les patients atteints de brucellose orientés par les principaux hôpitaux de Sanaa vers le Laboratoire de santé central pendant une période de deux ans 1992-1993 (235 adultes et enfants). Chaque patient a été interrogé sur ses antécédents et on a procédé à un examen clinique, à des tests de laboratoire généraux et des analyses de laboratoire pour la brucellose. Le tableau clinique général de la brucellose dans cette étude est très similaire à celui signalé par d'autres agents de santé dans cette zone géographique. La connaissance des signes de présentation et la prise de conscience du fait que la brucellose devrait faire partie du diagnostic différentiel pour les patients fébriles ayant une hépatomégalie, une splénomégalie et une tuméfaction ganglionnaire entraîneront une augmentation de l'indice de suspicion pour cette maladie.

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Introduction

Human brucellosis can be an acute or a chronic febrile illness and presents with a variety of manifestations after an incubation period, which can vary from 1 to 6 weeks or many months. The disease has long been recognized as a cause of persistent infection. Brucellosis may be difficult to distinguish clinically from a number of other infections. The symptoms of acute illness are fever (the most frequent symptom), chills, shivering, malaise, nausea, extreme fatigue, night sweats and loss of appetite persisting for 3 to 6 weeks [*1,2*]. Headache is another common symptom, as are muscle and joint pains [*3–5*]. About two-thirds of patients with *Brucella melitensis* infection show enlargement of the liver and spleen, often with superficial lymphadenopathy and sometimes accompanied by transient jaundice [*1,2,6*]. Cough may also be noted in acute disease, and gastrointestinal disturbances such as constipation, diarrhoea and abdominal pain are not uncommon [*7*]. About 80% of patients recover spontaneously, others develop complications in the acute stage or pass into an undulatingly state of ill health with apraxia. Evidence of localized disease may occur in the acute or more chronic phases, including arthritis, spondylitis, epididymo-orchitis, endocarditis and neurological involvement [*1,8–17*]. Arthritis and spondylitis may be particularly disabling [*18*]. Illness due to *B. melitensis* is more severe than the disease caused by other *Brucella* species. More males are affected than women and there is a tendency for the disease to be commoner in the second and third decades of life, but it should be noted that no age is immune to brucellosis. Nevertheless, the disease is both curable and preventable [*19,20*].

We aimed to study the clinical characteristics of brucellosis in the Republic of Yemen.

Methods

Brucellosis was diagnosed by the following criteria:

- Isolation of brucella organisms from blood, and/or
- Presence of antibodies against brucella (titre of ≥ 1:160 by standard tube agglutination test).
- A concurrent clinical syndrome consistent with brucellosis, i.e. at least fever plus fatigue and myalgia for 2 or more weeks continuously.
- The following investigations were normal or negative:
  - repeated blood film for malaria
  - urine examination for urinary tract infection
  - blood culture for other pathogenic organisms
  - stool culture for salmonellosis, shigellosis
  - serology for syphilis (VDRL, TPHA) and rheumatic fever (antistreptolysin-O titration or simple slide latex test).

Patients included all cases of brucellosis at the main hospitals in Sana'a who were referred to the Central Health Laboratory for microbiological and other pathological investigations over a 2-year period (1992–93).

A history was taken from all patients and a clinical examination of each person was carried out. The findings were recorded using a pre-designed questionnaire that noted the presenting symptoms.

General laboratory tests were done, including blood culture, differential blood count, erythrocyte sedimentation rate, haemoglobin, biochemistry (albumin, globulin and liver function tests), urine examination, stool examination, repeated blood film for malaria and serological tests for syphilis.

Specific brucella laboratory tests included blood culture, standard agglutination test (performed using standardized heat-killed phenolized smooth brucella antigen from the Public Health Laboratory Service, Collindale, United Kingdom), and 2-mercaptoethanol (2-ME) test.

Results

Over a 2-year period, 235 cases of brucellosis were identified. Of these, 132 cases were male and 103 female, giving a male:female ratio of 1.3:1.0. The patients' ages ranged from 1 year to 85 years with a mean of 25.6 years. Table 1 shows the age and sex distributions of the patients.

Patients were divided into two groups according to age, in order to compare the occurrence of symptoms, signs and laboratory data. Group 1 included 47 patients, 18 males and 29 females, under 15 years of age. Group 2 included the remaining 188 patients, 114 males and 74 females, aged over 15 years. The clinical and laboratory findings of the disease were then compared between the groups. The symptoms of the patients are summarized in Table 2. The mean duration of the illness was 4 weeks in group 1 and 8.4 weeks in group 2. The main signs and blood picture are given in Tables 3 and 4.

Discussion

Brucellosis is a disease with a non-specific manifestation; it can occur at any age and affect any organ [*1,14,21,22*]. The ratio of male to female cases was roughly equal in our sample (1.3:1), in contrast to previous studies that reported a predominance of males [*1,22*]. These data suggest that male and female exposure to the risk of infection is about the same, and that the activities associated with exposure are performed by both sexes or that they are exposed to the same reservoir of infected animals but at

Table 1 **Age and sex data of the 235 brucellosis patients in the Republic of Yemen**

Age (years)	Males		Females		Total	
	No.	%	No.	%	No.	%
< 15	18[a]	13.6	29[a]	28.2	47	20.0
> 15	114[a]	86.4	74[a]	71.8	188	80.0
> 15–25	41	31.1	30	29.1	71	30.2
> 25–35	36	27.3	26	25.2	62	26.4
> 35–45	22	16.7	11	10.7	33	14.0
> 45–55	8	6.1	6	5.8	14	6.0
> 55	7	5.3	1	1.0	8	3.4
Total	132	56.2	103	43.8	235	100

[a] $\chi^2 = 7.62$, $P < 0.01$.

different points in the cycle of contact. The mean age of 25.6 years in our patients was similar to that of 24.5 years reported from Kuwait [*1*]. There were statistically significant differences between the occurrence of disease in adults and children ($\chi^2 = 7.62$, $P < 0.01$). The majority (80%) of patients were over 15 years of age while 20% were children under 15 years. This is in contrast to Kambal et al. [*23*], whose patients were predominantly children, but similar to the findings of Yinnan et al. [*5*] and Shehabi et al. [*24*]. This might be related to differences in the activities of adults at work or at home.

The duration of the symptoms was shorter in children (mean of 4 weeks) than in adults (mean of 8.4 weeks). This may be because sick children receive medical attention at an earlier stage than adults. It also indicates that the disease is not severe and progressive in adults; they will wait for some time, perhaps hoping it will resolve spontaneously, before finally seeking medical attention.

The clinical presentation shown in Table 2 is roughly similar to that reported by Mohd [*4*] and Madkour et al. [*25*] in Sudan and Saudi Arabia. Fever was the most common symptom (100%) and the temperature usually showed diurnal variation, being high in the afternoon and evening and returning to normal in the morning, as observed by others [*1,2,9,25,26*]. Profuse

Table 2 **Symptoms in the 47 children and 188 adults with brucellosis in the Republic of Yemen**

Symptom	Children		Adults		χ^2	*P*-value
	No.	%	No.	%		
Diarrhoea	37	78.7	35	18.6	63.9	< 0.01
Nausea	36	76.6	104	55.3	7.0	< 0.01
Vomiting	30	63.8	44	23.4	1.1	> 0.05
Blood in stool	1	2.1	14	7.4	1.7	> 0.05
Abdominal pain	40	85.1	103	54.8	14.5	< 0.01
Body aches	36	76.6	181	96.3	20.5	< 0.01
Headache	23	48.9	151	80.3	19.3	< 0.01
Malaise	43	91.5	183	97.3	3.49	FET = 0.3
Weakness	37	78.7	128	68.1	2	> 0.05
Back pain	19	40.4	140	74.5	19.9	< 0.01
Sciatica	0	0	5	2.6	–	FET = 0.6
Joint pain	6	12.8	91	48.4	19.7	< 0.01
Joint swelling	3	6.4	37	19.7	4.7	< 0.05
Sore throat	6	12.8	12	6.4	2.17	> 0.05
Skin rash	2	4.2	9	4.8	–	FET = 0.6
Sweating	41	87.2	175	93.1	–	FET = 0.15
Fever	47	100	188	100	–	–

FET = Fisher exact test.

evening and night sweats are common features of brucellosis [*2,9,25*]. Sweating was associated with fever in 87.2% of children and 93.1% of adults, and was often profuse with a mouldy odour. This characteristic odour has been observed by Mousa et al. [*22*].

Gastrointestinal symptoms were more common in children than in adults and the differences were statistically significant (diarrhoea: $\chi^2 = 63.9$, $P < 0.01$; nausea: $\chi^2 = 7.0$, $P < 0.01$; abdominal pain: $\chi^2 = 14.5$, $P < 0.01$) (Table 2). In contrast Yinnan et al. [*5*] and Mousa et al. [*22*] found gastrointestinal symptoms to be predominant in adults. Moreover, in our study, gastrointestinal symptoms were more frequent than previously reported [*1,4,22–25*]. The most common gastrointestinal symptoms were nausea, abdominal pain and diarrhoea. Vomiting was less frequent.

Malaise and headache were more frequent in adults than in children, and the frequency was similar to that reported by Mohd [*4*]. Osteoarticular problems were more frequent in adults than in children, with back pain occurring in 74.5% of adults versus 40% of children ($\chi^2 = 19.9$, $P < 0.01$). This was less frequent than the 96% reported by Mohd [*4*], but more frequent than other reports by Mousa et al. [*25*] of 30%, Madkour et al. [*25*] of 56%, and Mousa et al. [*1*] of 11%. Joint pain and joint swelling were commoner in adults than in children (48.4% and 19.7% in adults versus 12.8% and 6.4% in children). It was less than the 56.6% to 86.2% reported by some others [*4,22,25*], but similar to the 40.4% found by Mousa et al. [*22*].

Skin rash is uncommon. Mousa et al. [*1*] noted this feature while Kambal et al. [*23*] did not report its occurrence. Skin rash occurred in 4.2% of children and 4.8% of adults in our sample.

Lymphadenopathy is a common physical finding in brucellosis. The prevalence in children (63.8%) was higher than in adults (26.6%), a statistically significant difference ($\chi^2 = 23.22$, $P < 0.01$) (Table 3). In our sample, the prevalence of lymphadenopathy was higher than that reported from Sudan [*4*] and Kuwait [*22*], but lower than that reported from Saudi Arabia [*25*]. Lymphadenopathy was a more frequent finding in patients who had had the disease for a short period than in those who had had it for longer. Thus, it is essential that brucellosis be considered an important cause of fever with lymph node enlargement, as are tuberculosis, visceral leishmaniasis and lymphoma. The frequency of hepatomegaly and splenomegaly were similar to the findings of Kambal et al. [*23*] and Mohd [*4*]. The diagnostic significance of splenomegaly and hepatomegaly is uncertain in

Table 3 **Signs observed in the 47 children and 188 adults with brucellosis in the Republic of Yemen**

Sign	Children		Adults		χ^2	*P*-value
	No.	%	No.	%		
Hepatomegaly	26	55.3	41	21.8	20.72	<0.01
Splenomegaly	37	78.7	53	28.2	40.63	<0.01
Arthritis	3	6.4	43	22.9	6.49	<0.05
Lymphadenopathy	30	63.8	50	26.6	23.22	<0.01

countries where other diseases that produce the same signs are common. In the Republic of Yemen, where malaria, schistosomiasis, chronic liver diseases due to hepatitis B and C and kala-azar are all common, hepatomegaly and splenomegaly have reduced diagnostic significance.

The reported frequency of brucella arthritis is highly variable, with figures ranging from 15% to 53% [*3,12,25,27*]. In our sample arthritis occurred in 6.4% of children and 22.9% of adults ($\chi^2 = 6.49$, $P < 0.05$) (Table 3), which is less than that reported in Saudi Arabia [*25*]. We found arthritis to be commoner in adults than in children, in contrast to the predominance of younger age groups reported in other countries [*28*].

Although haematological abnormalities due to brucellosis are well documented, they are of little diagnostic value. Schirger et al. [29] found anaemia in only 6% of the patients with brucellosis, and white blood cell count was normal in most of their brucellosis patients (78%). Other authors have reported a higher frequency of anaemia, leukopenia and thrombocytopenia, [*1,20,30–32*]. In our series of 235 patients with brucellosis, anaemia was mostly normocytic normochromic and was more common in children (72.3%) than adults (20.7%) ($\chi^2 = 46.74$, $P < 0.01$) (Table 4).

In acute or chronic brucellosis, the total white blood count is usually normal, but sometimes leukopenia or even leukocytosis may be present [*25,26*]. In our sample, leukopenia occurred in 63.8% of children and 16.5% of the adults ($\chi^2 = 43.8$, $P < 0.01$). Leukopenia is frequently accompanied by splenomegaly, and 93.4% of our patients with leukopenia also had splenomegaly.

Leukocytosis is infrequent in acute and subacute brucellosis. It occurred at roughly equal frequencies in children (12.8%) and adults (9.6%) in our study. This incidence is similar to that reported by Mousa et al. [*1*]. Some authors have emphasized the importance of relative lymphocytosis [*32*]. and this was a more common finding in our patients than in other reports in this

Table 4 **Blood picture of the 47 children and 188 adults with brucellosis in the Republic of Yemen**

Blood picture	Children		Adults		χ^2	*P*-value
	No.	%	No.	%		
Anaemia[a]	34	72.3	39	20.7	46.74	< 0.01
Leukopenia (< 4000 WBC/L)	30	63.8	31	16.5	43.83	< 0.01
Leukocytosis (> 100 000 WBC/L)	6	12.8	18	9.6	0.42	> 0.05
Lymphocytosis	20	42.5	108	57.4	3.36	> 0.05
Thrombocytopenia (<150 000 platelets/L)	4	8.5	0	0	–	FET = 0.001
Normal blood picture	6	12.8	56	29.8	7.17	< 0.01

[a]Anaemia was diagnosed if haemoglobin was < 13 g/dL (adult male), < 11 g/dL (adult female) and < 11 g/dL (child).
WBC = white blood cells.
FET = Fisher exact test.

area [*1*]. Thrombocytopenia was observed only in 4 children (8.5%), combined with splenomegaly. While the majority of patients with brucellosis are reported to have a normal haematological picture, only 29.8% of our adult patients and 12.8% of the children had a normal blood picture.

In countries where brucellosis is endemic, the disease can usually be diagnosed easily and rapidly both clinically and serologically, generally within 3 to 5 days [*20*]. In the Republic of Yemen, however, brucellosis is not commonly considered among the list of diseases that cause pyrexia as physicians are unfamiliar with its occurrence and epidemiology. They therefore do not request the relevant diagnostic laboratory investigations. A definitive diagnosis of brucellosis can be made only by identifying the etiological agent. But it can be difficult to isolate the organism from patients suffering from subacute or chronic forms of the disease, and the frequent prior use of antibiotics makes this even harder. In our sample, diagnosis was made on the basis of compatible clinical features, positive serology and/or blood culture. It has been suggested that cultures of bone marrow, liver, lymph node and other infected tissues improve diagnosis [*33*], but these samples could not be obtained from our patients because of technical difficulties. Only 16 patients (7%) had blood cultures positive for *B. melitensis* in spite of the repeated blood culture. The organism was grown after 1 week of incubation in 15 samples and after 4 weeks in one sample. Other investigations have reported a variation from 5% to 64% in the frequency of positive blood cultures [*1,20,24,29,33*]. The widespread availability of antibiotics and their use before diagnosis are important factors in reducing the yield of brucella cultures in our series. In our sample, 86% of the patients had taken antibiotics prior to collection of blood for culture.

The standard agglutination test (SAT) has been extensively evaluated for reproducibility and accuracy [*34*] and is still the most widely used test in serodiagnosis of human brucellosis. In our study we therefore relied on SAT to diagnose brucellosis, as have the majority of other studies [*1,32*]. While most authors agree that diagnosis of brucellosis can be established clinically and serologically, there is no agreement on the agglutination titre to be considered significant and indicative of active infection. Most authors take a titre of 1:160 as significant in a symptomatic patient [*24*]. In our study a titre of 1:160 with suggestive clinical symptoms was considered to be significant, while a high titre of brucella agglutinins in the absence of symptoms was not considered to indicate active disease. Our patients had titres ranging from 1:160 to 1:1280.

Treatment with 2-mercaptoethanol (2-ME) inactivates IgM antibodies, and so the residual titre after 2-ME treatment indicates the anti-brucella IgG and IgA titres. The 2-ME test has proved useful in those patients with disease of more acute onset, as well as those with more longstanding symptoms that may be due to brucellosis. A 2-ME agglutination of 1/20–1/40 would usually be indicative of active infection requiring treatment. Again, however, there are no established criteria to indicate what constitutes a significant titre [*35–37*]. Most of our patients had a positive 2-ME test with a titre of 1:20.

Conclusion

The overall clinical picture of brucellosis emerging from this study is very similar to that reported by other workers in this geographical area. There was not a marked difference in the male:female ratio of cases,

although what difference there was may relate to different activities carried out by the sexes leading to different exposures to infection risk. If clinicians are made more aware of the presenting features of brucellosis and that it should come into the differential diagnosis of fever associated with enlarged liver, spleen and lymph nodes, it will lead to an increasing index of suspicion for this infection. The availability of diagnostic laboratory tests such as those used in this study will provide sound criteria for diagnosis.

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