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# Epidemiological features and clinical manifestations in 469 adult patients with brucellosis in Babol, Northern Iran

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## SUMMARY

The epidemiological features and clinical manifestations of adult cases of brucellosis admitted to the Department of Infectious Diseases, Babol Medical University, Iran from 1997 to 2002 were investigated. Of 469 cases, 267 (56·9%) were males. The mean age of cases was $36{\cdot}9 \pm 15$ years. Most (60·8%) were from rural areas. Two thirds of cases (306, 66·3%) presented during spring or summer. Fresh cheese (22·4%), animal husbandry (11·3%), laboratory worker (8·1%) and veterinary profession (1·5%) were the main risk factors. Forty-five families (9·6%) had two cases. Sweating, fever, and arthralgia were the most frequent clinical symptoms. Complications were documented in 105 males (39·5%) and 41 females (20·3%, $P = 0{\cdot}0001$). Peripheral arthritis was seen in 24 (9%) males and 19 (9·4%) females, with knees and hips being the most common sites of infection. Sacroiliitis and spondylitis were seen in 28 (6%) and 32 (6·8%) cases respectively with spondylitis more common in males ($P = 0{\cdot}023$). Epididymo-orchitis was seen in 29 (10·9%) males. There were three cases each of endocarditis (0·6%) and neurological complications (0·6%). Most patients with brucellosis did not have any of the known risk factors for brucellosis. Thus consumption of unsafe dairy products could be the main route of infection. The disease manifested with a diversity of clinical manifestations and complications. Complications were more frequent in males than females.

## INTRODUCTION

Brucellosis is still an important public health problem and is endemic in many countries throughout the world including Iran [1–3]. The transmission of brucellae from infected animals to humans occurs either by occupational contact or the consumption of contaminated animal products, especially milk, cream, butter and fresh cheese [3, 4]. The disease is characterized by fever, arthralgia, sweating, back pain, malaise and anorexia. It often results in complications and the musculoskeletal system is frequently affected [1, 4–6]. The clinical manifestations of human brucellosis depend on various factors including the size of the infecting inoculum, the route of infection, the patient's age, the duration of the disease, the species of *Brucella* infecting the individual [5, 7]. In endemic regions, many cases occur in females. Although there are many reports on brucellosis in adulthood and children, only a few comprehensive studies have been carried out to investigate the different features of brucellosis between the sexes [8, 9]. The purpose of this study was to evaluate the epidemiological features

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Table 1. *Epidemiological findings in 469 adult cases of brucellosis in Babol, northern Iran*

| Characteristics of patients | Male ($n=267$) No. (%) | Female ($n=202$) No. (%) | Total ($n=469$) No. (%) |
|---|---|---|---|
| Mean age ± S.D. (yr) | 35·88 ± 15·45 | 38·42 ± 14·28 | 36·97 ± 15 |
| Resident | | | |
| Urban | 110 (41·2) | 74 (36·6) | 184 (39·2) |
| Rural | 157 (58·8) | 128 (63·4) | 285 (60·8) |
| Seasonal distribution | | | |
| Spring | 64 (24) | 54 (26·7) | 118 (25·2) |
| Summer | 115 (43·1) | 73 (36·1) | 188 (40·1) |
| Autumn | 56 (21) | 47 (23·3) | 103 (22) |
| Winter | 32 (12) | 28 (13·9) | 60 (12·8) |
| Risk factors | 110 (41·2) | 93 (46) | 203 (43·3) |
| Husbandry | 33 (12·4) | 20 (9·9) | 53 (11·3) |
| Fresh cheese | 58 (21·7) | 47 (23·3) | 105 (22·4) |
| Veterinarian | 7 (2·6) | 0 (0) | 7 (1·5) |
| Laboratory worker | 12 (4·5) | 26 (12·9) | 38 (8·1) |
| Without risk factor | 157 (58·8) | 109 (54) | 266 (56·7) |
| Brucellosis in other family members | 28 (10·4) | 17 (8·4) | 45 (9·6) |
| Clinical type | | | |
| Acute | 162 (60·8) | 93 (46) | 255 (54·4) |
| Subacute | 87 (32·6) | 92 (45·5) | 179 (38·2) |
| Chronic | 18 (6·7) | 17 (8·4) | 35 (7·4) |

and clinical manifestations of adult brucellosis in males and females in northern Iran.

## MATERIALS AND METHODS

Epidemiological, clinical and laboratory data relating to 469 consecutive adult cases of human brucellosis who attended the Department of Infectious Diseases of the Babol Medical University between January 1997 and January 2003 were investigated. The department serves more than 1·5 million people living in two cities, Babol and Amol, and the surrounding villages in the north of Iran.

The diagnosis of brucellosis was established by demonstrating a brucella titre of $\geqslant$1:320 in a standard tube agglutination test (STAT) and a titre of $\geqslant$1:160 in 2-mercaptoethanol (2-ME) for patients with clinical signs and symptoms compatible with brucellosis.

Peripheral arthritis was diagnosed by the finding of swelling, effusion and limitation of motion in an involved joint. Sacroiliitis was established by using X-ray in the prone position with confirmation by bone scan. Spondylitis was diagnosed using magnetic resonance imaging (MRI) and gallium scanning of the skeletal system. Epididymo-orchitis was diagnosed by finding swelling and tenderness of scrotal skin, testis and epididymis, with confirmation by sonography. Endocarditis was diagnosed by elevation of erythrocyte sedimentation rate (ESR), anaemia and cardiac murmur, and confirmed by the detection of vegetations using echo-cardiography. Meningitis was diagnosed by the presence of headache, neck stiffness and fever and confirmed if analysis of cerebral spinal fluid (CSF) showed an aseptic meningitis plus *Brucella* serological positivity by STAT and 2-ME in CSF.

Normal values for blood biochemistry were defined [10]. Data were analysed by SPSS software, version 10.0.5 (SPSS Inc., Chicago, IL, USA). The $\chi^2$ test and Fisher's exact tests (when appropriate) were used for categorical variables and Student's $t$ test was used to compare mean values.

## RESULTS

More males ($n=267$) than females ($n=202$) presented with brucellosis at our hospital. The male to female ratio was 1·32 (Table 1). The mean age of the patients was 37 years (range 16–90 years). Although female cases were slightly older than males (38·5 *vs.* 35·9 years), the difference was not significant ($P=0·063$). More cases were from rural (60·8%) than from urban (39·2%) areas. The number of cases (40·1%) peaked during the summer months.

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Table 2. *Clinical manifestations in 469 adult cases of brucellosis*

| Clinical symptoms and signs | Male ($n=267$) No. (%) | Female ($n=202$) No. (%) | Total ($n=469$) No. (%) |
|---|---|---|---|
| Sweating | 197 (73·8) | 160 (79·2) | 357 (76·1) |
| Fever | 178 (66·7) | 136 (67·3) | 314 (67) |
| Arthralgia | 125 (46·8) | 127 (62·9) | 252 (53·7) |
| Back pain | 93 (34·8) | 64 (31·7) | 157 (33·5) |
| Myalgia | 55 (20·6) | 52 (25·7) | 107 (22·8) |
| Chills | 60 (22·5) | 44 (21·8) | 104 (22·2) |
| Splenomegaly | 17 (6·4) | 10 (5) | 27 (5·8) |
| Uncomplicated | 162 (60·7) | 161 (79·7) | 323 (68·9) |
| Complicated brucellosis | 105 (39·3) | 41 (20·3) | 146 (31·1) |
| Peripheral arthritis | 24 (9) | 19 (9·4) | 43 (9·2) |
| Monoarticular arthritis | 16 (6) | 10 (5) | 26 (5·5) |
| Hip | 5 (1·9) | 4 (2) | 9 (1·9) |
| Knee | 10 (3·7) | 3 (1·5) | 13 (2·8) |
| Ankle | 0 (0) | 3 (1·5) | 3 (0·6) |
| Wrist | 1 (0·4) | 0 (0) | 1 (0·2) |
| Polyarthritis | 8 (3) | 9 (4·5) | 17 (5·5) |
| Bursitis | 1 (0·4) | 2 (1) | 3 (0·6) |
| Sternoclavicular arthritis | 2 (0·7) | 0 (0) | 2 (0·4) |
| Sacroiliitis | 19 (7·1) | 9 (4·5) | 28 (6) |
| Spondylitis | 24 (9) | 8 (4) | 32 (6·8) |
| Epididymo-orchitis | 29 (10·9) | 0 (0) | 29 (6·2) |
| Endocarditis | 3 (1·2) | 0 (0) | 3 (0·6) |
| Meningitis | 0 (0) | 1 (0·5) | 1 (0·2) |
| Bell's palsy | 1 (0·4) | 0 (0) | 1 (0·2) |
| Hemiparesis | 1 (0·4) | 0 (0) | 1 (0·2) |
| Icteric hepatitis | 1 (0·4) | 0 (0) | 1 (0·2) |
| Erythema nodosum | 0 (0) | 2 (1) | 2 (0·4) |

Total complications and spondylitis in males were higher than in females ($P<0·0001$ and $P<0·023$ respectively). Arthralgia in females was higher than in males ($P<0·0001$). Other clinical symptoms and signs between sexes were not significant.

Established risk factors for brucellosis were reported by 43·3% of the patients (Table 1). Table 1 also shows the distribution of risk factors (where present) for all cases, by gender, and by type of clinical presentation. On questioning, over half the cases denied any of the risk factors that were sought. In 45 cases (9·6%) another family member had brucellosis during the study period. Acute disease was seen significantly more often in men than in women ($P=0·007$). Conversely, subacute disease occurred significantly more often in women ($P=0·007$).

Clinical manifestations are detailed in Table 2. The most common symptoms were sweating, fever and arthralgia and the frequency of clinical symptoms was very similar for the two sexes. Complications were significantly more frequent in males ($P<0·0001$). Males had spondylitis more often than females ($P<0·023$). Complications were observed at all stages of illness but in females complications were much less frequently observed in patients with chronic disease. In males, complications were seen in 38·9% ($n=63$) of the patients with acute type of disease, 40·2% ($n=35$) with subacute, and 38·9% ($n=7$) with chronic disease. In females the figures were 23·7% ($n=22$), 19·6% ($n=18$) and 5·9% ($n=1$) respectively. Laboratory test results are presented in Table 3.

## DISCUSSION

Brucellosis remains an important public health problem in Iran, causing serious complications and significant morbidity. The commonest aetiological agent in our region is *B. melitensis* [2, 11]. The finding that males and females are affected equally is consistent with the results of other studies in endemic regions, where consumption of dairy products, and not occupational exposure is the most common route of infection [7–9]. This is in contrast with the gender distribution of cases in low-incidence countries where brucellosis is more common in adult males with an

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Table 3. *Laboratory test results on 469 adult cases of brucellosis*

| Laboratory test | Total No. (%) |
|---|---|
| WBC count | |
| <4000 | 14 (3·0) |
| 4000–9000 | 323 (68·9) |
| >9000 | 57 (12·2) |
| Platelet count | |
| Normal | 448 (95·5) |
| High | 5 (1·1) |
| Low | 16 (3·4) |
| Anaemia | 71 (15·1) |
| Positive CRP | 277 (59·1) |
| Normal ESR | 365 (77·8) |
| Positive RF | 40 (8·5) |

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; WBC, white blood cells.

occupational risk [3]. The seasonal distribution of diseases in our region is similar to that normally seen in endemic areas [9, 12–14]. The increased consumption of unsafe milk and milk products and ice creams as refreshments during the hot summer months may contribute to the higher proportion of cases in this period.

In this study, only a small fraction of the patients could be linked to common risk factors such as consumption of home-made fresh cheese, working with animals, or employment in a laboratory or as a veterinarian. Laboratory workers are at occupational risk of developing brucellosis in our region. The high risk of brucellosis in laboratory workers in this study is likely to be due to exposure to cultures or to blood samples from infected patients. The stage distribution of disease (acute, subacute or chronic) in our series was similar to that reported from Kuwait and Turkey [13–15]. Most patients (68·9%) had uncomplicated brucellosis with the main clinical symptoms being sweating, fever and arthralgia – similar findings to the results obtained by others working in endemic regions [8, 9, 13, 15, 16].

Brucellosis often results in complications and the musculoskeletal system is affected most frequently [4]. In the present study, there were more males (39·3%) than females (20·3%) with complications. Sacroiliitis and spondylitis were observed more frequently in men than in women. Some investigators have reported more severe forms of the disease in women [17]. The prevalence and pattern of musculoskeletal system involvement depends on the infecting strain of the bacterium and duration of the disease [5, 7, 8, 16, 18]. Infection of joints is the most frequent localized complication of brucellosis and one of the common causes of infectious arthritis in endemic regions [7, 19]. In our study, peripheral arthritis was seen in 34 cases (9·2%); arthritis was monoarticular in 26 cases (5·5%). Peripheral arthritis, seen in 42 cases (9·2%) was the most frequent type of osteoarthricular involvement in this study, a finding in agreement with reports of three other studies in endemic areas [6, 20, 21], although Geyik and co-workers [8] and Tasova and co-workers [7] reported a higher frequency of peripheral arthritis in their studies (30·7% and 19% respectively). In our study arthritis affected males and females equally. The different criteria used for the diagnosis of arthritis and the extended duration of the disease may explain these variations.

We found that the second most common site to be affected was the sacroiliac joint (6%). This proportion was comparable with the findings of several investigators [9, 21–23], but lower than those reported by others [5, 7, 8, 24]. A less common site of infection is the sternoclavicular joint. In our study, sternoclavicular arthritis was documented in two cases only. Brucellosis is a relative common cause of vertebral osteomyelitis in endemic areas [24–27]. Spondylitis was seen in 32 (6·8%) of our cases; other researchers have reported frequencies ranging from 8% to 13·8% [7, 13, 20, 28]. Spondylitis may be complicated by potentially devastating neurological defects that must be considered carefully in endemic areas [29, 30].

Epididymo-orchitis is another common manifestation of infection in brucellosis, occurring in up to 17·5% of patients [4, 31]. In our series it was documented in 29 (10·9%) cases. Epididymo-orchitis can give rise to serious complications such as necrotizing orchitis and must be considered in the differential diagnosis of acute scrotal inflammation in endemic areas [32–34]. The reported frequency of epididymo-orchitis has ranged from 1·6 to 17% across several studies [9, 12, 33–35]. Inappropriate diagnosis and management of this manifestation of the infection may result in serious complications in up to 39% of cases including testicular abscess formation, infarction, atrophy and suppurative necrosis [35–39]. The differential diagnosis of epididymo-orchitis requires a detailed history, meticulous physical examination and rapid laboratory evaluation. In *Brucella*-endemic areas, clinicians encountering epididymo-orchitis should consider the likelihood of this infection as a cause.

Infective endocarditis is the most catastrophic complication of brucellosis, seen frequently in

endemic regions. In our study, there were just three cases (0·5%) of *Brucella* infective endocarditis. Colmenero and colleagues [20] reported a frequency of 1·5% of infective endocarditis among 530 cases of brucellosis, similar to the results of our study. Memish & Venkatesh [12] and Namidura et al. [9] reported endocarditis in 1·8 and 6·8% of their cases respectively.

Nervous system involvement is seen in approximately 2–6·5% of brucellosis cases [1, 4]. In our study, neurological manifestations were seen in three (0·6%) cases. In 2003 Bodur et al. [40] reported neurobrucellosis in 17·8% of Turkish patients with brucellosis, and cranial nerve palsy was seen in three (4%) of their cases. This higher incidence may be explained by the fact that the Turkish study was performed in a referral hospital.

Hematological abnormalities, such as anaemia, leucopenia, and thrombocytopenia, are common in brucellosis [1, 4]. In our study, leucocytosis was found in 12·2%, anaemia in 15·1%, and thrombocytopenia in 3·4% of the cases. These findings were similar to those reported in several studies in Turkey [8, 9, 41], with the exception that anaemia that was seen more frequently than in our study. Proportions of patients in our study with positive CRP, positive RF and normal ESR were much lower than in other studies [7, 8, 24]. These differences may be due to early diagnosis of our patients after the onset of disease; 54·4% of our patients were diagnosed less than 2 months after the onset the disease.

In conclusion, the main route of transmission of brucellosis in our region is likely to be the consumption of unsafe dairy products. Brucellosis was observed with a diversity of clinical manifestations and complications. However, at the time of diagnosis, the majority of our patients presented with a combination of musculoskeletal manifestations, sweating and arthralgia. In *Brucella*-endemic regions, if this group of symptoms is present, brucellosis should be suspected.

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