Background: We conducted a retrospective cohort study to evaluate the clinical manifestations, laboratory findings, complications and treatment of brucellosis in the State of Qatar.

Methods: The medical records of patients in Hamad Medical Corporation, Doha, Qatar were reviewed from January 2000 to December 2006. History, various socio-demographic features, clinical and biochemical parameters, therapeutic features, and complications were retrospectively collected from the patient database.

Results: Around three quarters of the study population were males. History of raw milk consumption and animal contact were seen in 41.7% and 12.5% respectively. The main presenting features of our cohort were fever, chills and sweating (93.1%, 62.5% and 58.3% respectively). Positive antibody titre (≥1:160) was detected in 95.8% and positive blood culture was reported in 63.9% of the cohort. Splenomegaly was observed in 19.4%, hepatomegaly in 15.3% and lymphadenopathy in 9.7% of the cases. Approximately half of our patients were treated with a combination of doxycycline and streptomycin and nearly one quarter received doxycycline and rifampicin combination therapy.

Conclusions: Brucellosis is an important public health problem worldwide. It is associated with significant morbidity and mortality. It may affect any organ system and can present with a variety of clinical features. Diagnosis of brucellosis requires serological tests with or without blood culture. Treatment with at least two antibiotics for six weeks or more appears to be effective.

Keywords: Brucellosis, Middle East, Qatar, Malta fever
INTRODUCTION

Brucellosis is the most common bacterial zoonosis worldwide. It spreads throughout the world, with higher incidence rate in the Mediterranean region, Arabian Peninsula, Balkan Peninsula, India, and Central and South America. The incidence of human brucellosis in endemic areas varies widely, from <0.01 to >200 per 100,000 population. It is caused by Gram-negative bacteria called Brucella. There are four out of six species that infect humans. Among them Brucella melitensis is currently the most common species that infects human beings. The disease spreads to humans by the ingestion of raw dairy products, the consumption of infected animal meat and close contact with their secretions and carcasses. Camel milk is considered to be the most important source of the infection in Middle Eastern countries. Moreover, human to human transmission of Brucella infection has been reported.

Brucellosis mainly presents with high fever (sometimes named Malta or undulant fever), myalgia and arthralgia. Bone and joint involvement and epididymo-orchitis are considered the most frequent complications of brucellosis. Relapse of brucellosis is often seen because it is an intracellular organism. Diagnosis requires a high degree of clinical suspicion and thorough occupational and travel history. However, a definitive diagnosis requires isolation of Brucellae from blood and bone marrow samples and by detection of antigens and antibodies to Brucella by serological tests. Prevention of brucellosis is dependent mainly upon increasing public awareness, safe livestock practices and mass vaccination of animals. The treatment recommended by the World Health Organization (WHO) for acute brucellosis in adults is rifampicin 600 to 900 mg and doxycycline 100 mg twice daily for a minimum of six weeks. Combination of intramuscular streptomycin (1 g daily for 2 – 3 weeks) with an oral tetracycline (2 g daily for 6 weeks) gives fewer relapses. Tetracycline monotherapy for 6 weeks is a good option for patients with brucellosis with no focal disease and a low risk of relapse. Patients with focal disease, such as endocarditis or spondylitis, may require extended courses of antibiotics. Surgery should be considered for patients with endocarditis, and cerebral or spleen or hepatic abscess that are antibiotic resistant.

Increased business and travel have led to diagnostic challenges in non-endemic areas like the State of Qatar. The aim of this study was to report brucellosis in the State of Qatar, which is the first reported study in the country and to compare the clinical manifestations, laboratory findings and treatment with that in the literature.

METHODS

Population and design

A retrospective search of the computerized patient record system (Medicom) and patient files at Hamad Medical Corporation, Doha, Qatar was performed to identify patients with evidence of brucellosis from January 2000 to December 2006. Information on age, sex, occupation, history of raw milk ingestion, presenting symptoms and physical signs were collected. We also retrieved the results of routine laboratory tests, medications given, outcome and complications from the Medicom database and patients’ case notes at presentation. Patients less than 18 years of age were excluded from the study. However, a total of 72 patients were ultimately included in the study.

Diagnosis of Brucellosis was made based on the following criteria

(1) Compatible clinical features, namely fever, sweating, chills, headache, arthralgia and malaise, supported by the detection of specific antibodies at significant titres.
(2) Demonstration of four-fold rise in antibody titre in serum specimens. Antibody titre (≥ 1:160) in the standard tube agglutination test (STA) is considered to be significant and diagnostic for brucellosis.
(3) Isolation of Brucella spp. in blood.
(4) Focal form or complication was defined as the presence of symptoms or physical signs of infection at a particular anatomic site in a patient with active brucellosis.

Treatment

Patients were treated with single or combined antibiotic regimens including:

Oral doxycycline (100 mg every 12 h), oral rifampicin (300 or 600 mg every 24 h), intramuscular streptomycin (1 g every 24 h), oral ciprofloxacin (500 mg every 12 h) and co-trimoxazole (80/400 mg or 160/800 mg every 12 h). All patients were treated for 6 weeks and followed after discharge...
from the hospital till completion of the treatment course.

**Statistical Analyses**

Data were analysed using the Statistical Package for Social Sciences (SPSS, Inc., Chicago, IL, version 13.0.1). Descriptive statistics are presented as mean (standard deviation) for continuous data or number (percent) for categorical data.

**RESULTS**

**Demographic and clinical characteristics of study population**

As shown in Table 1, approximately 78% of the study patients ($n = 56$ out of $72$) were between 20 – 60 years old. Males made up more than $3/4$ of the study population. More than half of the participants had a history of risk factor for brucellosis. Of which, 41.7% had a history of raw milk consumption and 12.5% had history of animal contact. However, 45.8% of the cases had no documented risk factors. Merely 5.4% of the study population reported past history of brucellosis. The main presenting features were fever, chills and sweating, accounting for 93.1%, 62.5% and 58.3% respectively. Around one third of patients presented with generalized arthralgia, one quarter with cough and anorexia and one fifth with abdominal pain.

**Laboratory and clinical findings of brucellosis**

Around one third of patients had anemia ($\text{Hb} < 12 \text{ gm}\%$). Leukocytosis ($\text{WBC} > 11000/\mu\text{L}$) was detected in 6.9% with 77.8% and 52.8% of patients had lymphocytosis and neutrophilia respectively. An additional 16.7% had leucopenia. Elevated ESR ($> 30 \text{ mm/h}$) and CRP ($> 5 \text{ mg/l}$) were seen in approximately one third of the studied population (34.7% in each). Raised liver enzymes were found in 40% of the cases. However, positive antibody titre ($> 1:160$) and positive blood culture were detected in 95.8% and 63.9% respectively. The most frequent clinical finding was splenomegaly, it was seen in 14 cases (19.4%). Hepatomegaly and lymphadenopathy were seen in 15.3% and 9.7% of cases respectively. Spinal cord involvement (vertebral osteomyelitis) was found in 4.2% of patients, while psychosis was not reported in our cohort (Table 2).

**Treatment of Brucellosis**

Around half of the patients received a combination of doxycycline and streptomycin. Doxycycline and rifampicin combination were used in 22.2% of the cohort. However, other combination regimens were used to treat patients with brucellosis in this cohort (Table 3). Relapse and therapeutic failure of brucellosis were not detected in our cohort.

**DISCUSSION**

Brucellosis is an important public health problem that can cause serious complications and significant morbidity. In our cohort study, all age groups were susceptible to the infection and there was an obvious preponderance of males, as can be seen in Table 1, and this is in accordance with other studies (15,16). Consumption of raw milk and milk products and to a lesser extent contact with infected animals or their waste materials are the main routes of infection. There was a past history of brucellosis in some patients.
The clinical manifestations of brucellosis are protean. Most patients of our cohort had uncomplicated brucellosis with the main clinical symptoms being fever, night sweating, chills, arthralgia and loss of appetite. Moreover, hepatomegaly, splenomegaly, lymphadenopathy, and spinal cord involvement in the form of vertebral osteomyelitis were described in our series. Interestingly, neuropsychosis was not seen in our patients. The clinical characteristics of brucellosis in our cohort are similar to those reported by previous studies.(17)

Confirmation of brucellosis can be made with serological tests, with significantly high titer, in the presence or absence of blood culture. Brucella antibody titers (≥ 1:160) are suggestive of active infection. The serological tests sensitivity ranges from 65% to 95%, but their specificity is low because of the high prevalence of antibodies in the healthy population.(18) However, isolation of Brucella spp. from blood and other body fluid is the mainstay of diagnosis.(19)

In our cohort, antibody detection (positive antibody titer ≥1:160) was described in 95.8% and isolation of Brucella spp. from the blood was seen in 63.9% of the cases.

Anemia and raised ESR, CRP and liver enzymes were the most prominent laboratory abnormalities in our patients. Leukopenia was found in 12 cases (16.7%), leukocytosis in 5 cases (6.9%), and thrombocytopenia was seen in 13.9% of the cases.

Hematological alterations in brucellosis are common and include anemia, leukopenia, leukocytosis and thrombocytopenia. The incidence of anemia has been reported as 43.6% to 74% in brucellosis in adult patients. (21) In addition, anemia was reported in 44% in the study of Al-Eissa et al.(20) Earlier studies have emphasized the characteristic picture of a normal or reduced leucocyte count with relative or absolute lymphocytosis in patients with brucellosis.(20,21) Thrombocytopenia have been reported in only 1.7% to 15% of cases and it is rarely severe enough to cause bleeding. (22) In addition, pancytopenia has been described as between 2% to 14% in patients with brucellosis in the published series of Al-Eissa et al.(20) Hepatic involvement has been reported in around 2% to 3% of cases. (22) However, hepatitis is common, it is usually subclinical, and jaundice is rare. (23) A study from Kuwait by Lulu et al., reported around 40% hepatic involvements which include 1% clinical hepatitis and 38.5% anicteric hepatitis. (24) In our study, hepatomegaly was described in 15.3%, jaundice in 2.8% and raised liver enzymes in around 44% of cases.

Basically, treatment of brucellosis requires combinations of doxycycline with either rifampicin or streptomycin aiming to control the acute illness and to prevent both complications and relapses.
Since the study was retrospective, patients were treated with several therapeutic regimens for a total of six weeks. The most commonly used regimens in our study were doxycycline and streptomycin in 51.4% and doxycycline and rifampicin in 22.2% of the cohorts. This is in agreement with the standard of care.

CONCLUSION

In conclusion, brucellosis is a public health problem in countries with widespread use of dairy products and raw milk consumption. It has a significant morbidity and mortality. It may affect any organ system and can present with a variety of clinical entities. Diagnosis of brucellosis requires serological tests with or without blood culture. Treatment with at least two antibiotics for six weeks or more appears to be effective. Therefore, early diagnosis of the infection together with antibiotic treatment and long-term follow-up should improve the patient outcome.

REFERENCES

1. Pappas G, Papadimitriou P, Akritidis N, Christou L, Tsianos EV. The new global map of human brucellosis. *Lancet Infect Dis*. 2006;6:91 – 99.

2. Awad R. Human brucellosis in the Gaza strip, Palestine. *East Mediterr Health J*. 1998;4:225 – 233.

3. Naparstek E, Block CS, Slavin S. Transmission of brucellosis by bone marrow transplantation. *Lancet*. 1982;1(2871):574 – 575.

4. Lubani M, Sharda D, Helin I. Probable transmission of brucellosis from breast milk to a newborn. *Trop Geogr Med*. 1988;40(2):151 – 152.

5. Mantur BG, Mangalji SS, Mulimani M. Brucella melitensis – a sexually transmissible agent? *Lancet*. 1996;347(9017):1763.

6. Tikare NV, Mantur BG, Bidari RC, Mulimani MS, Veerappa, Kariholu P, Patil SB, Mangalgi SS. Protean clinical manifestations and diagnostic challenges of human brucellosis in adults: 16 years’ experience in an endemic area. *J Med Microbiol*. 2006;55 (Pt 7):897 – 903.

7. Solera J, Martinez-Alfaro E, Espinosa A, Castillejos ML, Geijo P, Rodriguez-Zapata M. Multivariate model for predicting relapse in human brucellosis. *J Infect Dis*. 1998;36:85 – 92.

8. Fallatah SM, Odulouju AJ, Al-Dusari SN, Fakunle YM. Human brucellosis in Northern Saudi Arabia. *Saudi Med J*. 2005;26(10):1562 – 1566.

9. Jennings GJ, Hajjeh RA, Girgis FY, Fadeel MA, Maksoud MA, Wasfy MO, El-Sayed N, Srikanthiah P, Luby SP, Earhart K, Mahoney FJ. Brucellosis as a cause of acute febrile illness in Egypt. *Trans R Soc Trop Med Hyg*. 2007;101(7):707 – 713.

10. Buzgan T, Karahocagil MK, Irmak H, Baran AI, Karsen H, Evirgen O, Akdeniz H. Clinical manifestations and complications in 1028 cases of brucellosis: a retrospective evaluation and review of the literature. *Int J Infect Dis*. 2010;14(6):e469 – e478.

11. Tanir G, Tufekci SB, Tuygun N. Presentation, complications, and treatment outcome of brucellosis in Turkish children. *Pediatr Int*. 2009;51:114 – 119.

12. Ulug M, Can-Ulug N, Selek Ç. Akut brusellozlu hastalarda akut faz reaktanlarinin düzyeti. *Klimik Dergisi*. 2010;23:48 – 50.
21. Dilek I, Durmus A, Karahocagil MK, Akdenyüz H, Karsen H, Baran AI, Evirgen Ö. Hematological complications in 787 cases of acute brucellosis in eastern Turkey. *Turk J Med Sci.* 2008;38:421–424.

22. Ertek M, Yazgi H, Kadanali A, Ozden K, Tasyaran MA. Complications of Brucella infection among adults: an 18-year retrospective evaluation. *Turk J Med Sci.* 2006;36:377–381.

23. Bukharie HA. Clinical features, complications and treatment outcome of Brucella infection: ten years' experience in an endemic area. *Trop J Pharm Res.* 2009;8:303–310.

24. Lulu AR, Araj GF, Khateeb MI, Mustafa MY, Yusuf AR, Fenech FF. Human brucellosis in Kuwait: a prospective study of 400 cases. *Q J Med.* 1988;66:39–54.