

1-1-2006

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ERTEK, MUSTAFA; YAZGI, HALİL; KADANALI, AYTEN; ÖZDEN, KEMALETTİN; and TAŞYARAN, MEHMET AKIN (2006) "Complications of Brucella Infection among Adults: An 18-Year Retrospective Evaluation," *Turkish Journal of Medical Sciences*: Vol. 36: No. 6, Article 10. Available at: <https://journals.tubitak.gov.tr/medical/vol36/iss6/10>

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Complications of *Brucella* Infection among Adults: An 18-Year Retrospective Evaluation

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Aim: Brucellosis is a systemic infection in which any organ or system of the body can be involved. We evaluate here complications and involvement of Brucella infection in Erzurum, Turkey.

Materials and Methods: We analyzed retrospectively 216 adult (89 female and 127 male) cases of brucellosis who were diagnosed and treated in the Infectious Disease Clinic of Atatürk University Research Hospital from 1985 to 2002. The diagnosis was based on clinical findings and serologic results and/or blood culture confirmations.

Results: All isolates from cultures were identified as *Brucella melitensis* biotype 1. Skeletal complications were the most frequent, found in 147 (68.1%) cases, followed by nervous system 9 (4.2%), cutaneous 9 (4.2%), genitourinary system 7 (5.5%), cardiovascular system 7 (3.2%), gastrointestinal system 7 (3.2%), and hematological system 6 (2.8%) complications.

Conclusions: Primary health care physicians should keep in mind the clinical and laboratory findings of Brucella complications.

Key Words: Brucellosis, complication, Brucella species, diagnosis

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Erişkinlerde *Brusella* İnfeksiyonlarının Komplikasyonları: 18 Yıllık Retrospektif Değerlendirme

Amaç: Brusellozis vücudtaki tüm organ ve sistemleri tutabilen sistemik bir enfeksiyondur. Çalışmamızda; Erzurum ve çevresindeki Brusellozlu olgularda görülen komplikasyonların değerlendirilmesi amaçlandı.

Yöntem ve Gereç: 1985-2002 yılları arasında Atatürk Üniversitesi Tıp fakültesi Araştırma Hastanesi İnfeksiyon Hastalıkları Kliniğine müracaat eden ve bruselloz tanısı konularak tedavi edilen 89 kadın ve 127 erkek olmak üzere toplam 216 hastada görülen komplikasyonlar retrospektif olarak değerlendirildi. Hastaların tanısı; klinik bulgular, serolojik test ve/veya kan kültürü sonuçlarına göre konuldu.

Bulgular: Tüm izolatlar *Brucella melitensis* biyotip 1 olarak saptandı. En sık komplikasyon görülme oranı kas iskelet sistemine aitti (147 olguda %68.1), bu oranı %5.5 (7 olgu) ile ürogenital sistem, %4.2 (9 olgu) ile santral sinir sistemi, %3.2 (7 olgu) ile kardiyovasküler sistem ve gastrointestinal sistem, %2.8 (6 olgu) ile hematolojik sistem izliyordu.

Sonuç: Tüm pratisyen ve uzman hekimlerin brusellozun komplikasyonlarının klinik ve laboratuvar bulguları konusunda dikkatli olmaları ve bu hastalığı hatırlamaları gereklidir.

Anahtar Sözcükler: Brusellozis, komplikasyon, Brucella türleri, tanı

Received: August 23, 2005
Accepted: December 07, 2006

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Introduction

Brucellosis is a zoonosis widely distributed around the world. In humans, brucellosis behaves as a systemic infection with a very heterogeneous clinical spectrum. The heaviest disease burden lies in countries of the Mediterranean basin and Arabian Peninsula, and the disease also occurs heavily in India, Mexico, and South and Central America. Disease incidence and prevalence rates vary widely among nations. Due to variable reporting, true estimates in endemic areas are unknown. Incidence rates of 1.2-70 cases per 100,000 people are reported (1). The incidence of this disease in Turkey is 23 per 100,000 per annum (source: Republic of Turkey, Ministry of Health, *Brucella* statistical data for 1970-2004) (2).

Brucella species are named for their primary host species and are further subdivided into biovars based on serologic agglutination with smooth lipopolysaccharide (S-LPS) associated

antigens M and A. *Brucella melitensis* is found primarily in goats and sheep, but may also be found in cattle because of indirect contact with infected sheep and goat flocks that have contaminated pastures from which fodder was harvested for lactating cows. *B. melitensis* is divided into three biovars (1-3). *Brucella abortus* is pathogenic for cattle, but can also infect sheep, goats, canines, horses and humans. The species is comprised of severe biovars (1-6 and 9). Biovars 7 and 8 are no longer valid. *Brucella suis* contains five biovars: biovars 1, 2 and 3 are found in swine, biovar 4 is found in reindeer and caribou in the arctic regions of North America and Russia, and biovar 5 causes infections in rodents. *Brucella canis* strains comprise a single biovar and occur in dogs. *B. abortus*, *B. melitensis*, *B. suis* and *B. canis* can cause infection in humans. Other species, *Brucella ovis* and *Brucella neotomae*, have not been shown to cause human infection. *B. melitensis* is considered the most virulent species, followed by *B. suis* and *B. abortus*. *B. canis* rarely causes infections in humans, and most infection has been acquired in the laboratory. The protean complications associated with *Brucella* infections are not generally seen in human *B. canis* infections (3,4).

The clinical features of brucellosis are not disease-specific; almost every organ can be affected. The prevalence and pattern of complications depend on the strain of *Brucella* infecting the individual and the duration of the disease (5). In this study, all patients with brucellosis were investigated in more detail with respect to complications, including skeletal, cardiovascular, pulmonary, abdominal, genitourinary, central nervous system (CNS), hematological and cutaneous.

Materials and Methods

The present study was retrospectively carried out at Atatürk University Medical Faculty Hospital, Department of Clinical Bacteriology and Infectious Diseases, between January 1985 and December 2002. Our hospital serves a population of 2.5 million inhabitants, and is the largest (1200-bed) hospital in the city of Erzurum in the Eastern Anatolian region of Turkey. The diagnostic criteria were a standard tube agglutination titer of 1/160 or more for anti-*Brucella* antibodies in the presence of compatible clinical findings (fever, night sweats, arthralgia, hepatomegaly, splenomegaly, and lymphadenopathy) and isolation of a *Brucella* spp. from blood or bone marrow cultures. The bacteria isolated from the cultures were

identified to the species level by using the following test: agglutination with the specific *B. abortus* and *B. melitensis* antisera, H₂S production, urea hydrolysis, and growth on media with basic fuchsin and thionine. All strains tested were identified as *B. melitensis* biotype 1. Sacroiliitis, spondylitis, peripheral arthritis, and orchitis were defined by appropriate findings on physical examination and relevant radiographic, radionuclide, and tomographic studies. All patients with suspected *Brucella endocarditis* were studied by transthoracic echocardiography, with the definitive clinical diagnosis made in accordance with Duke's criteria (6). Hepatic complications were defined as the presence of a five-fold or greater rise in normal levels of aspartate aminotransferase (AST) or alanine aminotransferase (ALT), or jaundice. In addition, completed history and physical examination of all patients were reviewed; tests for complete blood count, erythrocyte sedimentation rate, rheumatoid factor (RF), C-reactive protein (CRP), blood chemistry profile and urine analysis were performed in all patients. In suspected cases, lumbar puncture and bone marrow biopsy were performed for differential diagnosis of pancytopenia.

Results

In our study, 216 (127 male and 89 female) patients with brucellosis were analyzed. Signs and symptoms of brucellosis in this series reflected a combination of systemic illness with certain manifestations. Table 1 lists the main symptoms and signs noted on presentation. Arthralgia, malaise, sweating and fever were the main

Table 1. Clinical characteristics in 216 patients with brucellosis.

Symptoms	N %	Sign	N %
Arthralgia	181 (84)	Splenomegaly	76 (35)
Malaise	173 (80)	Hepatomegaly	58 (27)
Sweating	168 (78)	Lymphadenopathy	11 (5)
Anorexia	157 (73)	Heart murmur	4 (2)
Fever	156 (72)	Nuchal rigidity	5 (2)
Chills	148 (68)	Testicular swelling	7 (6)
Back pain	117 (54)	Rash	9 (4)
Headache	115 (53)	Jaundice	2 (1)
Myalgia	94 (43)		
Scrotal pain	7 (6)		

presenting symptoms overall. The commonest abnormalities on physical examination were fever (72%), hepatomegaly (27%) and splenomegaly (35%). Osteoarticular involvement was found in 147 patients (68.1%). Seven (6%) patients had orchiepididymitis involvement. Cutaneous, nervous, hepatitis, endocarditis, thrombophlebitis and hematological involvement were found in 9 (4.2%), 9 (4.2%), 7 (3.2%), 5 (2.3%), 2 (0.9%) and 6 (2.8%) patients, respectively. The commonest hematological abnormalities were thrombocytopenia (1.9%) and pancytopenia (0.9%).

According to the microbiological examinations, all isolates obtained from cultures were identified as *B. melitensis* biotype 1.

The most common complications were musculoskeletal and nervous system involvement and orchitis. In the skeletal system, sacroiliitis (56.2%) was the most common complication, followed by spondylitis (27.9%) and peripheral polyarthritis (21.3%). The other complications are shown in Table 2.

Discussion

Brucellosis complications are a major medical problem in countries where brucellosis is still endemic, as in our region of eastern Anatolia, Turkey. Among the four

species known to cause disease in humans, *B. melitensis* is the most virulent and causes the most severe and acute cases of brucellosis with disabling complications (1). Musculoskeletal involvement is seen as the most frequent complication of brucellosis; however, its prevalence may vary from 0% to 70% (7). The diversity of criteria used for the diagnosis of musculoskeletal involvement in brucellosis may cause variations in the results obtained by different researchers. Osteoarticular manifestations include peripheral arthritis, sacroiliitis, spondylitis, osteomyelitis, and bursitis (8,9).

In our study, the ratio of patients with musculoskeletal complications of brucellosis (68.1%) was very high. The most common skeletal complication was sacroiliitis, not osteomyelitis and bursitis. In countries where infection with *B. melitensis* predominates, the sacroiliac joint is the most frequently involved musculoskeletal site. Infection of the joints is the most frequent localized complication of brucellosis and a common cause of infectious arthritis in countries where the disease is endemic (7).

Meningitis, encephalitis, meningoenzephalitis, cerebellar ataxia, myelitis, radiculitis, peripheral neuritis, Guillain-Barré syndrome, and cranial nerve palsy have occurred in patients with brucellosis and involvement of the nervous system (10,11). Neurological involvement of the CNS has been detected in 2% to 5% of the patients with brucellosis, in both the presence and absence of systemic illness (12). Meningitis is the most frequent CNS complication (13). In the present study, meningitis was seen as a CNS complication (4.2%).

Cutaneous lesions occur in about 5% of patients with brucellosis. In the present study, cutaneous complications were the third most frequent (4.2%). The lesions were maculopapular and erythema nodosum. Cutaneous findings in our cases were similar to other reported studies (14-16). It is important to emphasize that cutaneous lesions are not specific to brucellosis and may be seen in a variety of other dermatologic diseases caused by many agents.

Cardiovascular localization of *Brucella* infection can result in endocarditis, myocarditis or pericarditis. The aortic valve has been commonly involved, followed by the mitral valve alone or both valves concurrently. The aortic valve is affected in 75% of patients, and 50% of affected valves were previously healthy. Despite its low frequency, endocarditis is a very severe complication of brucellosis,

Table 2. Complications in 216 patients with brucellosis.

Complications	N	%
Skeletal system	147	(68.1)
Spondylitis	63	(27.9)
Sacroiliitis	118	(56.2)
Peripheral monoarthritis	19	(8.8)
Peripheral polyarthritis	46	(21.3)
Nervous system	9	(4.2)
Cutaneous	9	(4.2)
Orchitis	7	(5.5)
Endocarditis	5	(2.3)
Thrombophlebitis	2	(0.9)
Hematologic	6	(2.8)
Thrombocytopenia	4	(1.9)
Pancytopenia	2	(0.9)
Gastrointestinal system		
Hepatitis	7	(3.2)

since its appearance is associated with a high mortality rate. Endocarditis was present in 80% of brucellosis patients who died, which highlights the importance of its suspicion in order to establish timely diagnosis. Endocarditis occurs in less than 2% of patients worldwide; however, in endemic areas, it may complicate 7%-10% of patients (17). In a previous study of 530 patients with brucellosis, only 6 (1.5%) had endocarditis (18). In the present study endocarditis was present in 7 patients (4.2%).

Epididymoorchitis is the most common genitourinary complication. Brucellosis is a relatively common cause of *Brucella* epididymoorchitis in geographic areas where *B. melitensis* is endemic. The incidence of epididymoorchitis in brucellosis is estimated at 2%-20% (19). Yurdakul et al. (20) reported a rate of 17% in their series and a study from India reported orchitis in 6 (6%) of 160 patients with brucellosis over a 12-year period (21). Khan (22) investigated 100 patients with brucellosis in Saudi Arabia and found testicular involvement in 6%. In the present study, epididymoorchitis occurred in 5.5% of all patients with brucellosis.

Liver involvement is frequently seen in brucellosis, although this involvement usually has little clinical importance and is usually limited to soft painless hepatomegaly, or slight increases in levels of aminotransferases. Liver abscess is uncommon in brucellosis. *Brucella* is also a rare cause of acute cholecystitis, pancreatitis and spontaneous bacterial

peritonitis (4). In this study, no cases of liver abscess, cholecystitis, pancreatitis or peritonitis were present, but 7 hepatitis (3.2%) cases were seen. Clinical features of these cases were those of viral hepatitis.

Mild hematological abnormalities, such as anemia and leukopenia, are common in the course of human brucellosis (23). Thrombocytopenia is less common, having been reported in only 1-8% of cases, and it is rarely severe enough to cause bleeding (24). Akdeniz et al. (25) reported that anemia was present in 128 patients (55%), leukopenia in 49 (21%), thrombocytopenia in 59 (26%) and pancytopenia in 18 (8%) patients. In another study, anemia was found in 74% of patients, leukopenia in 45%, neutropenia in 21%, lymphopenia in 63%, thrombocytopenia in 39.5%, and pancytopenia in 21% (26). In our study, thrombocytopenia was found in 4 patients (1.9%) and pancytopenia in 2 patients (0.9%).

The focal complications can affect any organ or system, which explains why these patients are not always seen by infectious disease specialists; therefore, many other medical and surgical specialists may diagnose the brucellosis. Even when there is a high degree of suspicion, the diagnosis of brucellosis is not always easy. Diagnosis of focal forms of brucellosis can occasionally be difficult, not only because the physician may not consider it as the cause of the clinical picture but also because even when it is considered, the yields of blood and non-blood sample cultures of patients with these forms are low.

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