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Original Article

Human brucellosis in Turkey: a review of the literature between 1990 and 2009

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Aim: Brucellosis is a systemic infection, which may involve any organ or system of the body. The aim of this study was a review of the literature related to human brucellosis in Turkey.

Materials and methods: In order to find the published reports on this subject, 3 national databases (TÜBİTAK-ULAKBİM Turkish Medical Literature database, http://www.turkishmedline.com, http://medline.pleksus.com.tr) and 2 international databases [Index Medicus and Science Citation Index (SCI)-expanded] were searched. In addition to the databases, abstracts of congresses held by the Turkish Clinical Microbiology and Infectious Diseases Association and the Antibiotic and Chemotherapy Association were searched for reports about brucellosis.

Results: The most frequent type of involvement was osteoarticular, followed by hematological abnormalities and nervous system involvement.

Conclusion: Brucellosis may present with a broad spectrum of clinical signs and symptoms. Primary health care physicians should be aware of the different clinical presentations of brucellosis.

Key words: Brucellosis, *Brucella* infection, neurobrucellosis, involvement, Turkey

Türkiye'de insan brusellozu: 1990 ve 2009 yılları arasındaki literatürün incelenmesi

Amaç: Bruselloz vücudun herhangi bir organını ya da sistemini tutabilen sistemik bir enfeksiyondur. Bu çalışmanın amacı, Türkiye'deki insan brusellozu ile ilgili literatürü incelemektir.

Yöntem ve gereç: Bildirileri bulmak için üç ulusal veritabanı (TÜBİTAK-ULAKBİM Türk Tıp Dizini veritabanı, http://www.turkishmedline.com, http://medline.pleksus.com.tr) ve iki uluslararası veritabanı [Index Medicus and Science Citation Index (SCI)-expanded] araştırıldı. Bu veritabanlarına ek olarak Türk Klinik Mikrobiyoloji ve Enfeksiyon Hastalıkları Derneği ve Antibiyotik ve Kemoterapi Derneği tarafından tutulan kongre özetleri, bruselloz hakkındaki bildiriler için araştırıldı.

Bulgular: En sık tutulum osteoartikuler sistem olarak belirlenirken hematolojik değişiklikler ve sinir sistemi tutulumu onu izlemektedir.

Sonuç: Bruselloz çok çeşitli klinik belirti ve bulgulara neden olabilir. Primer sağlık hizmeti veren hekimler brusellozun farklı klinik sunumlarının olabileceğini hatırında tutmalıdır.

Anahtar sözcükler: Bruselloz, *Brusella* enfeksiyonu, nörobruselloz, tutulum, Türkiye

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Introduction

Brucellosis is a zoonosis widely distributed around the world (1). Its high morbidity rate, both for animals and humans, is an important cause of economic losses and represents a serious public health problem in many developing countries (2). Brucellosis is endemic in Turkey and the annual incidence of the disease is 23 per 100,000 (3)

Brucellae are small gram-negative bacteria capable of surviving and even multiplying within the cells of the mononuclear phagocytic system, which may account for the prolonged course of the disease and high rate of complications and relapses (2). In humans, brucellosis manifests as a systemic infection with a very heterogeneous clinical spectrum (1). The clinical features of brucellosis are not disease-specific and almost every organ may be involved. This may result in the presentation of the patient to different specialists and a delay in diagnosis. In this study, all published series and case reports on brucellosis from Turkey were reviewed with respect to involvement sites to determine the various clinical presentations of brucellosis.

Materials and methods

Three national databases (Ulakbim, Turkish Medical Literature Database, http://www.turkishmedline.com, http://medline.pleksus.com.tr) and 2 international databases [Index Medicus and Science Citation Index-expanded (SCI-e)] were searched. The Ulakbim Turkish Medical Literature Database was founded by TÜBİTAK (The Scientific and Technological Research Council of Turkey) in 1996. Key words for national databases were "bruselloz", "*Brusella* enfeksiyonu", "*Brucella* infeksiyonu", or "nörobruselloz" and the key words for Index Medicus and SCI-e were [("brucellosis", "*Brucella* infection" or "neurobrucellosis") and Turkey]. Articles published before 1990 were excluded.

All published case reports and case series on Brucellosis were included in the study. In addition to the published articles extracted by the above-mentioned methods, abstracts presented in congresses held by the Turkish Clinical Microbiology and Infectious Diseases Association and the Antibiotic and Chemotherapy Association were searched for studies regarding brucellosis. All abstracts found either in databases or in congress abstract books were included. For studies that were both published and presented at congresses, only the published articles were considered.

Results

Data for 4204 patients with brucellosis were obtained from 306 reports (287 published articles and 19 congress abstracts). Sex (male/female) and median patient age could not be evaluated because they were not reported in some papers. Case reports were published from 38 provinces in Turkey. Ankara, İstanbul, and Van were the most frequently reporting cities for brucellosis.

The most common involvement was osteoarticular in 1839 patients (43.74%) followed by the hematopoietic system in 1401 (33.32%) patients. In decreasing order, nervous, gastrointestinal, urogenital, skin/mucous membrane, cardiovascular, respiratory system, and ocular involvement were reported in 413 (9.82%), 182 (4.32%), 171 (4.06%), 146 (3.47%), 67 (1.59%), 46 (1.09%), and 12 (0.28%) patients, respectively (Tables 1-9). Other, less frequent involvements are shown in Table 10.

Brucella spp. were isolated in 1311 patients (31.18%); 1019 patients (24.23%) had positive blood cultures. Other specimens that yielded bacterial growth with much lower isolation rates were bone marrow, cerebrospinal fluid, abscess material, ascites, operation material, synovial fluid, bronchoalveolar fluid, pleural fluid, semen, prostate gland fluid, and lachrymal gland fluid (Table 11).

Discussion

Brucellosis is a major medical problem in countries where brucellosis is still endemic, such as Turkey (1). Brucellosis is a systemic infection with a wide clinical spectrum, ranging from asymptomatic forms to severe cases causing death (1,2). Furthermore, it can affect virtually any organ or system, causing focal forms with prolonged clinical courses, which are considered true complications of the infection, creating an area of interest for all specialties.

Table 1. Involvement of the osteoarticular system.

Osteoarticular system	**n**	**%**
Sacroiliitis	723	17.19
Spondylodiscitis	546	12.98
Osteoarthritis	541	12.86
Osteomyelitis	8	0.19
Bursitis	8	0.19
Psoas abscess	5	0.11
Dactylitis	2	0.04
Spontaneous bone fracture	2	0.04
Tendinitis	1	0.02
Myositis	1	0.02
Intramedullary dermoid cyst abscess	1	0.02
Gluteal abscess	1	0.02
Total	**1839**	**43.74**

Table 2. Involvement of the haemopoietic system.

Hematopoietic system	**n**	**%**
Anemia	728	17.31
Thrombopenia	344	8.18
Leukopenia	229	5.44
Pancytopenia	76	1.80
Etiology of febrile neutropenia (accompanying hematological malignancies)	13	0.30
Microangiopathic hemolytic anemia	3	0.07
Autoimmune hemolytic anemia	3	0.07
Disseminated intravascular coagulation	3	0.07
Thrombotic thrombocytopenic purpura	2	0.04
Total	**1401**	**33.32**

Table 3. Involvement of the nervous system.

Nervous system	**n**	**%**
Meningoencephalitis	211	5.01
Major depression	46	1.09
Paravertebral abscess	26	0.61
Epidural abscess	26	0.61
Hearing loss	20	0.47
Abducens palsy	17	0.40
Papilledema	9	0.21
Polyradiculoneuritis	9	0.21
Brain abscess	5	0.11
Myelitis	5	0.11
Convulsion	4	0.09
Foot drop	4	0.09
Peripheral neuritis	3	0.07
Optic neuritis	3	0.07
Delirium	3	0.07
Pituitary gland granuloma	3	0.07
Spinal cord granuloma	3	0.07
Peripheral neuropathy	2	0.04
Ventriculoperitoneal shunt infection	2	0.04
Acute transverse myelitis	2	0.04
Prevertebral abscess	2	0.04
Acute psychosis	2	0.04
Extradural granuloma	1	0.02
Facial palsy	1	0.02
Guillain-Barré	1	0.02
Arachnoid cyst	1	0.02
Subdural hematoma	1	0.02
Cerebral infarct	1	0.02
Total	**413**	**9.82**

Table 4. Involvement of the gastrointestinal system.

Gastrointestinal system	**n**	**%**
Hepatitis	141	3.35
Spontaneous bacterial peritonitis	13	0.21
Splenic abscess	9	0.21
Acute abdominal pain	4	0.09
Ascites	3	0.07
Pancreatitis	2	0.04
Splenic pseudocyst	2	0.04
Acute cholecystitis (acalculous)	2	0.04
Ileitis	2	0.04
Hepatic abscess	2	0.04
Panniculitis	1	0.02
Splenic hematoma	1	0.02
Total	**182**	**4.32**

Table 5. Involvement of the urogenital system.

Urogenital system	**n**	**%**
Epididymo-orchitis	132	3.13
Chronic renal failure	8	0.19
Prostatitis	7	0.16
Pyelonephritis	6	0.14
Testicular abscess	4	0.09
Breast abscess	3	0.07
Ovarian abscess	2	0.04
Spontaneous abortus	2	0.04
Hematuria	2	0.04
Glomerulonephritis	2	0.04
Renal abscess	1	0.02
Acute renal failure	1	0.02
Bilateral mastitis	1	0.02
Total	**171**	**4.06**

Table 6. Involvement of the skin/mucous membrane.

Skin/mucous membrane	**n**	**%**
Maculopapular rash	86	2.04
Petechiae/purpura/ecchymosis	30	0.71
Thrombophlebitis	7	0.16
Erythema nodosum	5	0.11
Subcutaneous abscess	5	0.11
Malar rash	3	0.07
Psoriatiform rash	2	0.04
Palmar erythema	2	0.04
Palmar eczema	1	0.02
Livedo reticularis	1	0.02
Enanthem	1	0.02
Leucoclastic vasculitis	1	0.02
Pityriasis rosea	1	0.02
Diffuse rash	1	0.02
Total	**146**	**3.47**

Table 7. Involvement of the cardiovascular system.

Cardiovascular system	**n**	**%**
Endocarditis	51	1.21
Mycotic aneurysm	6 (3 patients with subarachnoid hemorrhage)	0.14
Pancarditis	5	0.11
Pericarditis	4	0.09
Capillary leak syndrome	1	0.02
Total	**67**	**1.59**

Table 8. Involvement of the respiratory system.

Respiratory system	**n**	**%**
Pneumonia	16	0.38
Pleuritis	14	0.33
Parenchymal granuloma	9	0.21
Bronchitis	5	0.11
Paratracheal lymphadenopathy	1	0.02
Acute respiratory distress syndrome	1	0.02
Total	**46**	**1.09**

Table 9. Ocular involvement.

Ocular involvement	**n**	**%**
Uveitis	5	0.11
Episcleritis	3	0.07
Optic neuropathy/blindness	2	0.04
Dermoid tumor in eyelid	1	0.02
Dacryoadenitis	1	0.02
Total	**12**	**0.28**

Table 10. Other involvements.

Involvement	**n**	**%**
Isolated cervical lymphadenopathy	1	0.02
Thyroiditis	4	0.09
Sepsis	3	0.07

Table 11. Isolation of *Brucella* spp. from several cultures.

Culture	**n**	**%**
Blood	1019	24.23
Bone marrow	200	4.75
Cerebrospinal fluid (CSF)	39	0.92
Abscess	17	0.40
Ascites	10	0.23
Tissue (operation material)	10	0.23
Synovial fluid	9	0.21
Prostate gland fluid	2	0.04
Bronchoalveolar lavage fluid	2	0.04
Pleural fluid	1	0.02
Semen	1	0.02
Lachrymal gland fluid	1	0.02
Total	**1311**	**31.18**

Notable discrepancies exist in the incidence rate and clinical spectrum of focal forms, making diagnosis challenging. Thus, the most common clinical forms of brucellosis and rare involvement sites should be recognized by clinicians. The osteoarticular system is the most common site of involvement in many series, as was the case in our series (1,2,4), with striking differences in the reported incidence, ranging from 0% to 72.5% (1,2,4-7). Our data rating sacroiliitis (17.19%) as the most common complication, followed by spondylodiscitis (12.98%) and osteoarthritis (12.86%), are in accordance with the findings of others (1,2,5). As is the case for other forms of brucellosis, the clinical features of osteoarticular complications are rather nonspecific. The presence of some suggestive symptoms, such as remitting fever, chills, sweating, and the involvement of the axial skeleton, allows the clinician to consider brucellosis when facing a differential diagnosis.

Hematological abnormalities were reported in 33.32% of cases in our series. Mild hematological

abnormalities, such as anemia and leukopenia, are common in the course of human brucellosis, and pancytopenia may develop in a small population (8), which was 1.80% in our series. However, although rare, severe forms such as disseminated intravascular coagulopathy may also develop. The pathogenesis of pancytopenia in brucellosis is not clearly understood, but seems to be multifactorial. Several possible mechanisms have been suggested for pancytopenia caused by brucellosis, such as hemophagocytosis, hypersplenism, bone marrow granulomas, bone marrow hypoplasia, and immune destruction (8). Hematological abnormalities occurring during the course of the disease may be misdiagnosed as hematological malignancies (8). In reports from Turkey, *Brucella* spp. were suggested to be the cause of febrile neutropenia in 13 patients with hematological malignancies (9 patients with acute lymphoblastic leukemia, 2 patients with acute myeloblastic leukemia, and 2 patients with multiple myeloma) in whom neutropenia was initially attributed to chemotherapy but was later found to be due to brucellosis. In these patients, the diagnosis of acute brucellosis was established incidentally by serum agglutination tests, and blood and bone marrow cultures that were performed on admission for the differential diagnosis of pancytopenia. Due to the slow growth of *Brucella* spp. in blood and bone marrow cultures and to the late appearance of clinical manifestations, empirical antibiotic therapy for febrile neutropenia may not yield favorable results in immunocompromised hosts (9). Thus, brucellosis should be considered a possible cause of febrile neutropenia, especially in endemic areas.

The 9.82% incidence of nervous system involvement in the present study lies somewhere between the reported incidence in other studies ranging from 0% to 25% (2,10). As expected, meningoencephalitis was the most common (5.01%) presentation, interestingly followed by depression, which underlines the significance of meticulous etiologic examination in psychiatric patients. In other reports, meningoencephalitis, brain abscess, acute transverse myelitis, polyradiculoneuritis, peripheral neuritis, Guillain-Barré syndrome, epidural and pre-paravertebral abscesses, and cranial nerve palsy have also been detected in patients with neurobrucellosis (1,2,4,10).

The lesions in neurobrucellosis are located mainly in the meninges, where a diffuse inflammatory infiltrate can be observed extending to the perineurium of the nerve sheaths and to the vessel walls. These pathologic findings explain the wide clinical polymorphism of neurobrucellosis (2). Although infrequent, neurological involvements are of marked clinical importance due to their severity and serious sequelae (2).

Brucellosis is a relatively common cause of epididymo-orchitis in geographic areas where *B. melitensis* is endemic. Epididymo-orchitis was the most common urogenital form in our study (3.13%), as in many other reports with an incidence ranging from 2% to 20% (11-14). Brucella epididymo-orchitis, in contrast to nonspecific epididymo-orchitis, frequently has associated systemic symptoms, minimal urinary symptoms and fewer alterations in the urine sediment (2).

The marked affinity of different *Brucella* spp. in the reproductive systems of cows, goats, and sheep is well established (2). The tropism for the genital organs of ruminants is suggested to be associated with high concentrations of erythritol (2). Despite lack of bacteriological or serological evidence for abortion in humans, 2 patients were reported with abortion during pregnancy in our study; however, it is not possible to clarify the actual cause of abortion in those patients.

The most common cutaneous lesions were maculopapular rash (2.04%) and petechie/purpura/ecchymosis (0.71%), which are not specific to brucellosis and may develop in a number of other conditions of infectious or noninfectious etiology, which may result in misdiagnosis. The pathogenic mechanism involved in cutaneous lesions of brucellosis can be multiple. Lesions produced by direct inoculation, hypersensitivity, deposition of immune complexes, and direct invasion of the skin from the blood have been reported (15).

Cardiac involvement in brucellosis is rare, occurring at a rate of 0% to 2% in large series (2), and 1.59% in our study. Endocarditis is the most common cardiovascular complication and most importantly, a large proportion of cases, more than 50% in some series, involve a previously healthy native valve (2), which was also confirmed by our data with 35/51

(68.62%) cases with endocarditis with previously healthy native valves. The aortic valve is the most commonly involved, followed by the mitral valve alone or concurrently (2). However, it was not possible to report the most common site of involvement in our study because the localization of valvular involvement was not reported in most studies.

Brucellosis rarely causes gastrointestinal, pulmonary and ocular involvements, isolated lymphadenopathy, and thyroiditis (1,2).

Brucellosis can affect any system, resulting in the involvement of clinicians from many different specialties, which may account for the high rate of late diagnoses and misdiagnoses. Thus, clinicians must develop a high degree of clinical suspicion based on epidemiological and clinical information for early and prompt diagnosis. The diagnosis of brucellosis requires microbiological confirmation by isolation from blood culture or the detection of specific antibodies by serological tests. Although the isolation of Brucella spp. from cultures is considered the gold standard (16,17), the isolation rate may be low as in the present study (31.18%), probably due to previous antibiotic use and the unavailability of results for several weeks due to the fastidious growth of the microorganism. Thus, serologic methods are an important tool for early diagnosis, especially in endemic areas.

In conclusion, the diagnosis of brucellosis, which is an endemic disease in Turkey, is challenging due to the various clinical presentations, and leads to labor loss due to serious complications; thus, it should be considered in the differential diagnosis of numerous diseases.

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