Evaluation of Brucellosis Patients Followed-up in a Tertiary Hospital

Üçüncü Basamak Bir Hastanede İzlenen Brusellozis Olgularının Değerlendirilmesi

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Öz

Amaç: Brusellozis Türkiye'de endemik olarak görülen aynı zamanda halk sağlığı problemi olan zoonotik bir infeksiyondur. Bu çalışmada kliniğimizde takip edilen brusellozis olgularının demografik/epidemiyolojik, klinik, laboratuvar özelliklerinin, komplikasyon ve tedavilerinin değerlendirilmesi amaçlanmıştır.
Hastalar ve Yöntem: Bu çalışmada kliniğimizde 1 Ocak 2010-31 Aralık 2018 tarihleri arasında takip edilen olguların özellikleri retrospektif olarak incelendi. Tanımlayıcı veriler sayı ve yüzde (%) olarak belirtildi. Kategorik değişkenler ki-kare testi, sayısal değişkenler Student-T testi kullanılarak analiz edildi.
Bulgular: Toplam 365 brusellozisli hastanın 159 (%43.56)'u kadın, 206 (%56.44)'sı erkekti. Hastaların yaş ortalaması 45.9±14.51 (18-82) idi. En sık başvuru zamanı 137 (%37.5) ile yaz mevsimiydi. Hastalığın en sık 252 (%69) bulaş yolu hayvancılıkla uğraşma öyküsü olarak bulundu. Olguların 168 (%46)'i akut, 96 (%26.3)'sı subakut, 101 (%27.7)'i kronik brusellozis idi. Hastaların en sık şikayeti 302 (%82.7) halsizlik olup akut brusellozste daha yüksekti (0.0015). Elli üç (%33.3) erkek, 114 (%55.3) kadında anemi olup kadınlarda anemi daha yüksek (p=0.0283) bulundu. Hastalarda %7.9 lökopeni, %16.2 lökositoz, %9.6 trombositopeni, %4.1 nötropeni, %9 nötrofili, %12 lenfomonositoz saptandı. Wright agglütinasyon testi 26 (%7.1), Brusella immuncapture aglütinasyon testi 361 (%98.9) hastada bakılmış olup hepsinde pozitif saptandı. Hastaların 172 (%47.1)'sinde komplikasyon gelişip en sık 58 (%15.9) spondilodiskit saptandı. Olguların 61(%31.8)'inde relaps gelişti.
Sonuç: Brusellozisin ülkemizde endemik olması nedeniyle halsizlik, eklem ağrısı ve ateş gibi şikayetler ile başvuran hastalarda brusellozis ön tanılar arasında yer almalıdır.

Anahtar Kelimeler: Bruselloz, epidemiyoloji, klinik, laboratuvar, komplikasyon, tedavi

Abstract

Aim: Brucellosis is a zoonotic infection seen as an endemic in Turkey and is a public health problem at the same time. The objective of this study was to evaluate demographic/epidemiologic, clinic, laboratory features, complications and treatments in brucellosis patients followed-up in our clinic.
Patients and Methods: In this study, features of patients followed-up between 01/01/2010 and 31/12/2018 in our clinic were retrospectively evaluated. Descriptive data were expressed as number and percentage. Categorical variables were analyzed with Chi-square test and numerical variables with Student's t test.
Results: Of the total of 365 brucellosis patients, 159 (43.56%) were female and 206 (56.44%) were male. The mean age of the patients was 45.9±14.51 (18-82) years. The most common time of presentation was summer season with 137 (37.5%) patients. The most common transmission route of the disease was a history of animal husbandry with 252 (69%) patients. Of all cases 168 (46%) were acute, 96 (26.3%) were subacute, and 101 (27.7%) were chronic brucellosis. The most common complaint of the patients was fatigue in 302 (82.7%) patients with being higher in acute brucellosis (p=0.0015). Anemia was found in 53 (33.3%) male and 114 (55.3%) female patients with being significantly higher in female patients (p=0.0283). Leukopenia was found in 7.9%, leukocytosis in 16.2%, thrombocytopenia in 9.6%, neutropenia in 4.1%, neutrophilia in 9% and lymphomonocytosis in 12% of the patients. Wright agglutination test was performed in 26 (7.1%) and brucella immunocapture agglutination test in 361 (98.9%) patients and all results were positive. Of all patients, 172 (47.1%) developed complications with spondylodiscitis being the most commonly found in 58 (15.9%) patients. Sixty-one (31.8%) of patients developed relapse.
Conclusion: Since brucellosis is endemic in our country, it should be considered in presumed diagnosis of patients presenting with complaints such as fatigue, articular pain and fever.

Key words: Brucellosis, epidemiology, clinic, laboratory, complication, treatment

INTRODUCTION

Brucellosis (also known as undulant fever, Malta fever or Mediteranean fever) is one of the common infectious zoonotic diseases worldwide. The World Health Organization (WHO) points out that 500,000 human brucellosis cases occurs annually worldwide, and the disease causes danger for public health in many developing countries (1).

The most common route of transmission to humans is the consumption of unpasteurized dairy products (especially raw milk, cheese, butter). Inhalation of bacteria that cause brucellosis can also lead to infection. This risk is generally higher in people working with bacteria in laboratories. In addition, slaughterhouse workers, meat packaging facility workers and veterinarians are at risk due to close contact with animals or animal wastes (newborn animals, fetuses and wastes from delivery) (2). Human brucellosis is an important zoonosis with its high prevalence worldwide and especially in the Middle East, Central Asia and Mediterranean regions (3). In our country, 4475 cases have been reported in 2014, 4173 in 2015, and 5148 in 2016. However, 6457 cases were seen in parallel with the increase in animal cases in 2017 (4). In a multicenter seroprevalence study conducted in Turkey, the seropositivity rate was 1.8% in healthy individuals, while this rate was found as 6% in high-risk groups (veterinarians, farmers, etc.) (5). In Turkey, brucellosis is a disease seen in all regions. It is especially most common in East and Southeast Anatolia. The incidence of brucellosis was found as 12.9% in Konya province in 2017 (4).

Our country is an endemic region of brucellosis, and this disease remains a serious public health problem. Therefore, the objective of this study was to evaluate demographic/epidemiologic, clinic and laboratory features, complications and treatments in brucellosis patients aged between 18-80 years who presented from Konya and its surroundings and were followed-up in our clinic between 2010 and 2018.

PATIENTS AND METHODS

Before the beginning of the study, the necessary ethics approval was received from the local ethics committee of the university (Necmettin Erbakan University, Faculty of Meram Medicine, 2019/1674 number decision). Brucellosis cases aged ≥ 18 years who were followed-up and treated in our clinic between 01/01/2010 and 31/12/2018 were retrospectively evaluated. Patient' data were obtained through patient files from the archive and hospital automation system. Patients' demographic features, risk factors for brucellosis (husbandry, consumption of raw milk and village cheese), complaints of admission, complete blood count at the time of the first presentation, sedimentation rate (SED), C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT) values and serologic features, treatment administered, and presence of complications and relapse were recorded. The diagnosis of brucellosis was established in the presence of clinical finding with detection of a titer ≥ 1/160 in standard tube agglutination (STA) test or at least 4 folds increase in antibody titers in two serum samples collected with 2 weeks intervals, or titers ≥ 1/320 in immunocapture agglutination test (BCAP) or isolation of Brucella spp. from blood and/or other sterile body fluids. Automated blood culture system was used for the isolation of Brucella spp. from blood, bone marrow, synovial fluid and other samples. Vitek 2 (biomerieux) automated system was used for the identification and antibiotic sensitivity of the isolates. Blood culture bottles of the patients considered to have brucellosis were kept for one month. Patients with symptom onset < 8 weeks were considered to have acute, those with symptom onset between 8-52 weeks subacute, and patients with symptom onset longer than one year as chronic brucellosis. Complications were diagnosed with radiologic imaging methods (Ultrasonography, Magnetic Resonance Imaging etc.). The diagnosis of neurobrucellosis was based on abnormal findings of cerebrospinal fluid (CSF) or STA positivity in any titer in CSF. Cerebral Computed Tomography and Magnetic Resonance Imaging (MRI) examinations were performed when deemed necessary. In genitourinary complications the diagnosis was established with physical examination and scrotal ultrasonography (USG) in necessary cases. Considering clinical findings and complications, combinations of 2 or 3 antibiotics were administered in patients. Occurrence of similar symptoms and findings in any period within one year after the completion of the treatment was evaluated as relapse. Data were analyzed with SPSS (Statistical Package for the Social Sciences) version 22.0 statistical software. Descriptive data were expressed as number and percentage. Categorical variables were compared with Chi-square test and numerical variables with Student's t test. p<0.05 values were considered statistically significant.

Table 1. Distribution of complaints between the groups

	Acute n=168(%)	Subacute n=96(%)	Chronic n=101(%)	Total n=365(%)	P value
Fatigue	152(90.5)	73(76)	77(76.2)	302(82.7)	0.001
Joint pain	130(77.4)	68(70.8)	74(73.3)	272(74.5)	0.474
Fever	100(59.5)	44(45.8)	50(49.5)	194(53.2)	0.069
Lower back pain	74(44)	49(51)	48(47.5)	171(46.9)	0.542
Sweating	85(50.6)	39(40.6)	41(40.6)	165(45.2)	0.161
Anorexia	70(41.7)	32(33.3)	34(33.7)	136(37.3)	0.274
Weight loss	61(36.3)	28(29.2)	26(25.7)	115(31.5)	0.166
Hip pain	32(19)	28(29.2)	31(30.7)	91(24.9)	0.055
Nausea	29(17.3)	16(16.7)	17(16.8)	62(17)	0.918
Cough	11(6.5)	4(4.2)	1(1)	16(4.4)	0.097

RESULTS

Of the 365 brucellosis patients, 159 (43.56%) were female and 206 (56.44%) were male. The mean age of all patients was 45.9±14.51 (18-82) years. The mean age was found as 48.47±13.76 years in female patients and 43.92±14.8 years in male patients. The mean age was statistically significantly higher in female than in male patients (p=0.0029). The most common time of presentation was summer season with 137 (37.5%) patients followed by spring with 96 (26.3%) patients, fall with 73 (20%) patients and winter with 59 (16.2%) patients. The most common transmission route of the disease was a history of animal husbandry with 252 (69%) patients, followed by consumption of dairy products (cheese and ice cream made from raw milk etc.) with 68 (18.6%) patients, and occupational risk with 13 (3.6%) patients (veterinarians, butchers, laboratory workers etc.). The route of transmission could not be determined in 32 (8.8%) patients. Of all cases 168 (46%) were acute, 96 (26.3%) were subacute, and 101 (27.7%) were chronic brucellosis. Patients in all three groups presented with similar symptoms. The most common complaint was fatigue by 302 (82.7%). The distribution of admission complaints of the patients is shown in Table 1.

Elevated urea was found in 28 (7.7%) and elevated creatinine in 16 (4.4%) of all patients. Anemia was found in 53 (33.3%) males and 92 (44.6%) females and the difference was statistically significant higher in female (p=0.028). Laboratory findings of the patients are given in Table 2.

STA test was studied in 26 patients and found positive in 1/160 titer in 5 (19.3%) patients, 1/320 titer in 7 (26.9%) patients, 1/640 titer in 1 (3.8%) patient and 1/1280 titer in 1 (3.8%) patient. BCAP test was studied in 361 patients and found positive in 1/160 titer in 40 (11.1%), 1/320 titer in 59 (16.3%), 1/640 titer in 63 (17.5%), 1/1280 titer in 55 (15.2%), 1/2560 titer in 48 (13.3%) and 1/5120 titer in 96 (26.6%) patients. Blood culture was taken in 90 patients and no growth was observed in 63 (70%) of these patients. Brucella spp. was isolated in 25 (27.8%) patients with one being synovial fluid, one in both blood and

Table 2. Laboratory findings of the patients

	Acute n=168(%)	Subacute n=96(%)	Chronic n=101(%)	Total n=365(%)	P value
Anemia	72(42.9)	36(37.5)	37(36.7)	145(39.7)	0.949
CRP ≥5 mg/L	116(69)	58(60.4)	66(65.3)	240(65.8)	0.362
SED ≥20 mm/saat	72(42.9)	43(44.8)	46(45.5)	161(44.1)	0.901
WBC <4000/µl	17(10.1)	7(7.3)	5(5)	29(7.9)	
≥10000/µl	22(13.1)	17(17.7)	20(19.8)	59(16.2)	0.383
Neutrophils<1500/µl	9(5.4)	4(4.2)	2(2)	15(4.1)	
Neutrophils ≥7300	13(7.7)	10(10.4)	10(9.9)	33(9)	0.626
Lymphocytes<800/µl	2(1.2)	2(2.1)	6(5.9)	10(2.7)	0.062
Monocytes ≥900	21(12.5)	7(7.3)	6(5.9)	34(9.3)	0.146
Platelets<150000/µl	18(10.7)	10(10.4)	9(8.9)	35(9.6)	0.889
ALT ≥40 U/lt	62(36.9)	22(22.9)	25(24.8)	109(29.9)	0.024
AST ≥40 U/lt	53(31.5)	20(20.8)	19(18.8)	92(25.2)	0.034

CRP;C-Reactive Protein SED; Sedimentation WBC; White Blood Cell ALT; Alanine aminotransferase AST; Aspartate aminotransferase

Table 3. Distribution of initial treatments

	n(%)
Doxycycline + rifampicin	154(42.2)
Doxycycline + streptomycin / gentamicin	139(38.1)
Doxycycline + streptomycin / gentamicin + rifampicin	42(11.6)
Doxycycline + ceftriaxone + rifampicin	11(3)
Seftriakson + rifampicin + SXT*	8(2.2)
Doxycycline + rifampicin + SXT*	4(1.1)
Doxycycline + rifampicin + ciprofloxacin	3(0.8)
Doxycycline + SXT*	2(0.5)
Doxycycline + ceftriaxone + SXT*	2(0.5)

*SXT; Trimethoprim sulfamethoxazole

paravertebral abscess material collected during the operation. No growth was found in CSF cultures of the patients with neurobrucellosis.

Complications were found in 172 (47.1%) patients. The most commonly seen complication was spondylodiscitis in 58 (15.9%) patients followed by arthritis in 26 (7.1%) patients, sacroiliitis in 18 (4.9%) patients, orchitis in 17 (4.7%) patients, hepatosplenomegaly in 14 (3.8%) patients, splenomegaly in 16 (4.4%) patients, neurobrucellosis in 7 (1.9%), hepatomegaly in 5 (1.4%) patients, lymphadenopathy in 4 (1.1%) patients, sternoclavicular abscess in 2 (0.5%) patients and tenosynovitis, infective endocarditis and abscess in the spleen and orchitis, hair loss and portal vein thrombosis and infarct in the spleen, uveitis and spondylodiscitis and sacroileitis in one each patient. The most commonly used combination for the treatment was doxycycline plus rifampicin in 153 (44.2%) patients. The distribution of initial treatments is shown in Table 3.

The most common side effects of the treatment were gastrointestinal system adverse effects in 27 (7.4%) patients, while nausea was seen in 9 patients, esophagitis in 6 patients, allergic reaction in 3 patients, diarrhea in 2 patients, gastric pain, hemorrhoid, and vaginitis in each one patients with doxycycline containing combination and nausea/vomiting was observed in 4 patients, and hepatitis in 4 patients with rifampicin containing combination. Since ototoxic side effects were seen in 9 patients with streptomycin, the drug was stopped in some patients with hearing loss. Allergic reaction with itching was seen in one each patient who received ceftriaxone and ciprofloxacin. Sixty-one (31.8%) of 192 patients developed relapse.

DISCUSSION
Brucellosis is a zoonotic, systemic, inflammatory disease especially seen in Mediterranean, which frequently affects young and middle-aged people in endemic areas (6,7). In a study by Turker et al. (8), all patients were in the middle-age group. In our study, the mean age of the patients was 45.9±11.51, which suggests that brucellosis affects the productive age group, causing significant morbidity and labour loss, and giving harm to the country's economy. Brucellosis shows a similar distribution in both sexes, although it usually influences men especially in the Mediterranean and Middle East countries (9). In a study by Ulug et al. (10), 59% of the patients were female, while in a study by Dal et al. (11), 69.2% of the patients were male, and in a study by Turker et al. (8) 51.6% of the patients were male. In our study, 56.44% of the patients were male, which can be attributed to that men usually more commonly work in animal husbandry.

The incidence of the disease increases in spring and summer months, because people more commonly travel to rural areas and obtaining fresh cheese and cream-like fresh butter from milk and dairy products increases (12). In a study by Ulug et al. (10), 83% of the cases were identified in spring and summer months (10). Similarly, in our study the most common time of presentation was found as summer season by 37.53% followed by spring at 26.3%. Brucellosis is most commonly the disease of farm workers, veterinarians, laboratory and slaughterhouse workers. However, transmission may also occur through the consumption of unpasteurized dairy products (3). Ulug et al. (10) found that 32% of the patients were engaged in a profession that could pose a risk for brucellosis, while this rate was reported as 25.4% by Yuce et al. (13), 15.7% by Gursoy et al. (14), and 44% by Dal et al. (11). In a study by Dal et al. (11), there was a history of the consumption of contaminated milk and dairy products in 93% of the cases. In the present study, the most common route of transmission was found as a history of husbandry by 69% followed by

the consumption of milk and dairy products (cheese and ice cream made from raw milk) by 18.6%, while 3.6% of the patients were found to have occupational risks (veterinarians, butchers, laboratory workers etc.). Transmission routes could not be found in 8.8% of the patients. This can be explained by the fact that our hospital is a tertiary hospital and patients present from Konya province as well as surrounding provinces such as Karaman and Aksaray. In addition, with incidental cannula sticks, brucellosis may be developed with vaccine strains of Brucella abortus or Brucella melitensis in veterinarians (3). Therefore, a combination of doxycycline and rifampicin was administered in two veterinarians as prophylactic in our hospital, and the disease disappeared. In a study by Demiroglu et al. (15), a similar prophylaxis was given to a veterinarian, but later the disease was seen.

Brucellosis can be clinically classified as acute, subacute and chronic disease. It can also manifest as a localized infection with an insidious onset (6,16). Dal et al. (11) found acute disease in 85%, and chronic disease in 3.3% of the patients. In our study, the most common form of brucellosis was acute with 45.2%, followed by chronic with 27.7% and subacute with 27.1%.

In a study by Kurtaran et al. (7), the most common form was acute brucellosis with more prominent symptoms being seen during this period. Although there was no difference between the disease phase and arthritis, arthralgia, splenomegaly, hepatomegaly and weight loss, fever was more common in acute disease than in other forms. Hepatomegaly and splenomegaly were not observed in chronic form of the disease In our study, fatigue was more common in the acute phase, while there was no difference between the disease phase and the other symptoms during study period.

Nonspecific symptoms and clinical findings that may be confused with many diseases can be seen in brucellosis (6). In a study by Gursoy et al. (14), main clinical symptoms included fever, arthralgia, sweating and fatigue, while fever was found in 61.2% followed by lymphadenopathy in 11.4%, splenomegaly in 10.7%, hepatomegaly in 8.6% and arthritis in 5.7% of the patients. In a study by Dal et al. (11), fever was observed in 95%, sweating in 90%, and lower back pain in 63% of the patients. In a study by Turker et al. (8), the most common clinical finding was fever by 51.6%. In addition, hepatomegaly was found in 27.9%, splenomegaly in 15.9%, lymhodenopaty

in 3.6% and pulmonary findings in 3.4% of the patients. In our study, the most commonly observed symptom was fatigue by 82.7% followed by articular pain by 74.5% and fever by 53.2%. The difference between the clinical findings might be resulted from different disease stages and personal factors. Affinity of Brucella spp. bacteria against mononuclear-phagocytic is high. Therefore, reticuloendothelial system organs such as liver and spleen are often involved (17). In our study, hepatosplenomegaly was found in 14 (3.8%), splenomegaly in 16 (4.4%) and splenomegaly in 5 (1.4%) patients. Respiratory system findings are infrequent in brucellosis (15). In our study, cough was found in 16 (4.4%) patients.

Mild anemia and leukopenia are common in brucellosis. However, isolated thrombocytopenia and pancytopenia are less common. These complications are usually seen in acute infection (18). In a study by Turker et al. (8), anemia was seen by 31%, leukopenia by 14.5% and thrombocytopenia by 10.9%. Leukocytosis (especially in those with focal complications), leukopenia, thrombocytopenia and anemia can be observed as laboratory findings in patients (19). In our study, anemia was found in 167 (45.8%) patients with leukopenia was found in 7.9%, leukocytosis in 16.2%, thrombocytopenia in 9.6%, neutropenia in 4.1%, neutrophilia in 9%, and lymphomonocytosis in 12% of the patients.

In general, a mild-to-moderate increase may be seen in SED and CRP (9). In a study by Turker et al. (8), elevated SED was seen by 61.6% and elevated CRP by 39% in all cases. In our study, SED was elevated in 44.1% and CRP in 65.8% of the patients.

Liver involvement, which can range from mild to severe disease, is common in brucellosis. (20). Liver enzymes are either normal or moderately elevated (21). In our study, AST was elevated in 25.2% and ALT in 29.9% of the patients.

STA test is the most commonly used method in serologic diagnosis of brucellosis worldwide (22). STA positivity was found as 94.3% in the study by Turker et al. (8) and 92% in the study by Dal et al. (11). In a study by Aydostlu et al. (23), STA was found as positive in 72% of the positive (≥ 1/160) . In our study, STA test was studied in 26 patients and found positive in 1/160 titer in 5 (19.3%) patients, 1/320 titer in 7 (26.9%) patients, 1/640 titer in 1 (3.8%) patient and 1/1280 titer in 1 (3.8%) patient. BCAP test was studied in 361 patients and found as positive in 1/160 titer in 40 (11.1%), 1/320 titer in 59 (16.3%), 1/640 titer in 63 (17.5%), 1/1280 titer in 55 (15.2%), 1/2560 titer

in 48 (13.3%) and 1/5120 titer in 96 (26.6%) patients. It is seen that the BCAP test is ordered much more commonly compared to the STA test in our hospital. This prevents the presence of blocking antibodies and prozone effects.

The ideal diagnosis for brucellosis is the isolation of causative agents from blood, bone marrow, liver biopsy material and other body fluids and/or tissues (24). Blood culture positivity was found as 22.4% by Turker et al. (8) and 31% by Dal et al (11). In our study, growth was observed in blood cultures of 25 (27.8%) patients, and Brucella spp. was isolated from knee synovial fluid in one patient and from both blood and paravertebral abscess material collected during the operation in another patient. In our study, lower rate of culture positivity might be caused by previous antibiotic use. Osteoarticular system is the most commonly involved system in brucellosis (25). In a study by Turker et al. (8), osteoarticular involvement was found by 29%, with spondylodiscitis was found by 18%, vertebral abscess by 4.6%, sacroiliitis by 3.9%, and arthritis by 2.5%. In a study by Dal et al. (11), 42.8% of the patients developed complications with the most common complication being osteoarticular involvement by 82%. In a study by Kurtaran et al. (7), peripheral arthritis was found in 4%, spondylitis in 22% and sacroiliitis in 27.1% of the patients. In the present study, the most common complication was found as spondylodiscitis in 58 (15.9%) patients, followed by arthritis in 26 (7.1%) patients, sacroiliitis in 18 (4.9%) patients, lymphadenopathy in 4 (1.1%) patients, abscess in the sternoclavicular joint in 2 (0.5%) patients and tenosynovitis in one patient (0.3%).

Neurological involvement is seen in approximately 10% of cases and is a serious complication of brucellosis (6). In a study by Turker et al. (8), meningitis was found by 8.3% (8). In a study by Dal et al. (11), central nervous system involvement was observed by 8%. In a study by Kurtaran et al. (7), neurobrucellosis was found in 12 (3.8%) of 317 patients. In our study, neurobrucellosis was found in 7 (1.9%) patients. The incidence of genitourinary system involvement is between 5-10% in brucellosis with most common complication being epididymoorchitis (6). Epididymoorchitis was found in 10% of patients by Dal et al. (11), 8.6% of patients by Turunc et al. (26), while orchitis was found in 5.2% of patients by Turker et al. (8). In our study, orchitis was found in 17 (4.7%) patients. In a study by Turker et al. (8), endocarditis was found by 2.5%, and pneumonia by 2.7%. In our study, tenosynovitis, infective endocarditis and abscess in the spleen and orchitis, hair loss, portal vein thrombosis and infarct in the spleen, uveitis and spondylodiscitis and sacroileitis were found in one each patient.

Treatment adherence of the patient and combined antibiotics therapy are important for success of the treatment. In the combined treatment, doxycycline and streptomycin are the best options especially in acute and localized forms. Since intramuscular administration of streptomycin for 3 weeks during the treatments of 6 weeks or longer leads to difficulties in application, alternative treatments has become a current issue. Six-week doxycycline with 7-day gentamicin (5 mg/Kg) is one of these alternatives. Today, according to the recommendations rifampicin (600-900 mg/day, oral) is administered together with doxycycline (200 mg/day, oral) for 6 weeks. However, it is emphasized that the effect of this treatment may be low compared to the treatment with streptomycin (27). In our country, the combination of doxycycline and rifampicin was found as 54.5% by Aypak et al. (28) and 77% by Kurtaran et al. (7). In our study, the most commonly used initial combination was doxycycline plus rifampicin by 42.2% followed by streptomycin and doxycyclin. It is known that doxycycline and streptomycin are more effective in bone-joint involvement of brucellosis (29). In the present study, aminoglycoside combination therapy was administered to 181 (49.6%) patients, and these patients were followed-up for autotoxicity during the treatment process, while 9 (5%) patients developed autotoxicity. The rate of this side effects was found as 9.1% with streptomycin combination by Yuce et al. (13), and 2.3% by Tulek et al. (30).

In a study by Demiroglu et al. (15), the most common side effect was gastrointestinal intolerance with 9 (6%) cases. This effect was observed to be resulted from doxycycline. In our study, the most common side effects were gastrointestinal adverse events in 27 (7.4%) patients, and these effects were thought to be often caused by doxycycline. The patients were advised to take the medicine with water, to not lie after taking the drug, to sit or to walk; and the medicine was changed in the case of continuing complaints despite this application. The rates of failed treatment and relapse are high in humans (27). Post-treatment relapse may be seen in approximately 10% of brucellosis patients (13). Dal et al. (11) found this rate as 5.4%. In the present study, 61 (31.8%) of 192 patients developed relapse. The groups could not be

compared in terms of treatment failure and relapse since the treatment groups were not homogenous.

It was found that brucellosis remains a serious problem in our region. The disease should be kept in mind in patients presenting with nonspecific symptoms such as fever, fatigue, and articular pain. In order to prevent and reduce brucellosis; cattles and sheep should be vaccinated, persons who contact with animals in risk groups should wear protective equipment such as gloves, and safety goggles, raw milk and dairy products should not be used without pasteurization, and public should be educated on this issues.

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