International Journal of Infectious Diseases 14 (2010) e469–e478

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Review

Clinical manifestations and complications in 1028 cases of brucellosis: a retrospective evaluation and review of the literature

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ARTICLE INFO

Article history:
Received 3 November 2008
Received in revised form 2 June 2009
Accepted 25 June 2009

Corresponding Editor:
William Cameron, Ottawa, Canada

Keywords:
Brucellosis
Epidemiology
Clinical finding
Laboratory finding
Complication

SUMMARY

Introduction: Brucellosis is the most prevalent bacterial zoonosis worldwide. In this study, we aimed to compare our 1028 brucellosis cases with other big series in the literature in view of epidemiological, clinical, and laboratory findings and therapeutic features.
Methods: A total of 1028 brucellosis cases admitted to the Department of Infectious Diseases and Clinical Microbiology over a 10-year period were included in the study. A retrospective analysis was undertaken and patient files were reviewed for history, clinical and laboratory findings, and therapeutic features, as well as complications.
Results: Of the 1028 patients, 539 (52.4%) were female and 489 (47.6%) were male. The mean age of patients was 33.7 ± 16.34 years and 69.6% of cases were aged 13–44 years. Four hundred and thirty-five cases (42.3%) had a history of raising livestock and 55.2% of the cases were found to have no occupational risk for brucellosis. Six hundred and fifty-four of the cases (63.6%) had a history of raw milk and dairy products consumption. The most frequently seen symptoms were arthralgia (73.7%) and fever (72.2%), while the most common clinical findings were fever (28.8%) and hepatomegaly (20.6%). The most frequent laboratory finding was a high C-reactive protein level (58.4%). The standard tube agglutination (STA) test + Coombs STA test was positive in 1016 cases (98.8%). Focal involvement was present in 371 (36.1%) cases. The most frequent involvement was osteoarticular involvement with 260 cases (25.3%). The overall relapse rate for patients with brucellosis was 4.7%. The highest relapse rate, 8.5%, was observed in the group of patients with osteoarticular involvement. Regimens including doxycycline and streptomycin with or without rifampin appeared more effective than other regimens in osteoarticular involvement.
Conclusions: In humans, brucellosis may lead to serious morbidity, and it continues to be a major health problem in Turkey. There is no recommended treatment protocol for complicated brucellosis. Large multicenter studies are needed to determine the most appropriate treatment choices and durations in complicated brucellosis.

Introduction

Brucellosis is a zoonosis caused by Gram-negative bacteria, *Brucella spp*. The disease spreads to humans by the ingestion of raw dairy products, the consumption of infected meat from domestic livestock (sheep, goats, cattle, water buffalo, camels and pigs) and close contact with their secretions and carcasses. High fever, myalgia, and arthralgia of the large joints are the main symptoms. Brucellosis usually causes abortion and sterility in animals, while it may lead to a variety of clinical presentations, such as fever and septicemia, and even multiple organ involvement, in humans.[1,2] Because brucellosis is one of the great imitators in the world of infectious diseases, it can mimic various multisystem diseases, showing wide clinical polymorphism, which frequently leads to misdiagnosis and treatment delays, further increasing the complication rates.[1,2] Clinically it may progress as a subclinical, acute, subacute or chronic infection. Since *Brucella spp* are intracellular bacteria, relapse is often seen.[1–4]

Human brucellosis remains the most common zoonotic disease worldwide, with more than 500 000 new cases annually. Its prevalence is more than 10/100 000 population in some endemic

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doi:10.1016/j.ijid.2009.06.031

countries.[5] Although it is seen widely throughout the world, it is hyperendemic in the Mediterranean Basin and Arabian Peninsula, India, Mexico, and Central and South America. Brucellosis has been eradicated in England, in many northern European countries, and in Australia, New Zealand, and Canada.[5,6]

In Turkey, brucellosis is common, especially in the Middle, East and Southeast Anatolia regions.[2,7] According to reports from the Turkish Ministry of Health, 37 cases were reported in 1970, with numbers rising to 18 408 cases in 2004 (incidence rate 25.67/100 000).[2,8] It is thought that this increase is a result of improvements in diagnosis and increased reporting, rather than a real increase in the prevalence of the disease.

The aim of this study was to report our brucellosis cases, which represent the largest series in the literature, and to compare our epidemiological, clinical, and laboratory findings and therapeutic features with reports of other large series.

Materials and methods

A total of 1028 brucellosis cases admitted to our clinic, the Department of Infectious Diseases and Clinical Microbiology of Yuzuncu Yil University Hospital, over a 10-year period from January 1998 to September 2007, were included in the study. A retrospective study was undertaken and patient files were investigated for their history, clinical and laboratory findings, as well as clinical outcomes and complications.

Brucellosis was diagnosed on the basis of one of the following criteria: (1) isolation of *Brucella spp* in blood, bone marrow, or cerebrospinal fluid (CSF) and other body fluids or tissue samples; (2) a compatible clinical picture, such as arthralgia, fever, sweating, chills, headache, and malaise, supported by the detection of specific antibodies at significant titers and/or the demonstration of an at least four-fold rise in antibody titer in serum specimens taken over 2 or 3 weeks. Significant titers were those determined to be $\geq$1/160 in the standard tube agglutination test (STA).[9] An adequate response to anti-brucellosis therapy was also accepted for diagnosis in those who were seronegative and showed no growth of Brucella. *Brucella abortus* M101 (Cromatest, Linear Chemicals, Spain) or *B. abortus* S99 antigens (Pendik Veterinary Control and Research Institution, Istanbul, Turkey) were used for the STA. Serologic tests were all carried out according to previously described techniques. Screening was done by slide agglutination or Rose Bengal plate agglutination test (Pendik Veterinary Control and Research Institution, Istanbul).[10]

Cases were divided into three groups according to their history, symptoms, and clinical presentation time: acute brucellosis (0–2 months), subacute brucellosis (2–12 months), and chronic brucellosis (>12 months). All cases underwent routine laboratory tests. Blood, bone marrow, CSF, arthrocentesis fluid, and abscess cultures were taken from patients depending on their clinical findings. Up until December 2004, cultures were identified by automated culture identification system, BACTEC 9240 (Becton–Dickson Diagnostic Instrument System, Franklin Lakes, NJ, USA); after that time the Phoenix Diagnostic System (Sparks, MD, USA) was used. The isolates were identified by CO_2 requirement, H_2S production, urease and oxidase positivity, growth in thionine, and positive agglutination with specific antiserum (Pendik Veterinary Control and Research Institution, Istanbul, Turkey).[11,12]

Radiologic examinations, such as plain X-ray, ultrasound (USG), computerized tomography (CT), magnetic resonance imaging (MRI), and echocardiography were done when needed for investigating the complications. A cranial CT was done for all neurobrucellosis cases, while electroencephalography (EEG) was done only in those whose encephalitis findings were dominant.

Definitions

'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.

'Osteoarticular involvement' was considered when there were inflammatory signs (heat, redness, pain, swelling, or functional disability) in any peripheral joint, or when there was unrelieved pain at rest together with radiological alterations and/or radionuclide uptake in any deep joint, evaluated independently by both the clinician and the radiologist.

'Neurobrucellosis' was defined as: isolation of *Brucella spp* from CSF of patients with suspected findings for brucellosis; or isolation of *Brucella spp* from bone marrow or blood cultures of patients with abnormal CSF findings; with or without STA positivity of any titer in CSF with abnormal findings.

'Hepatic involvement' was defined as a five-fold increase (>200 IU/l) in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels without any other etiologic explanation, and/or total bilirubin levels of over 2.5 g/dl.

'Hematologic involvement' was defined as hematologic abnormalities in laboratory and clinical findings (epistaxis, bleeding, petechiae, purpura, disseminated intravascular coagulation (DIC), and thrombophlebitis), excluding asymptomatic or poorly symptomatic cytopenias or coagulation disturbances.

'Relapse' was defined as the reappearance of symptoms or a positive blood culture after the treatment was concluded.[13]

Treatment and follow-up

Patients were treated with various combinations of antibiotics. The regimens included the following: oral doxycycline (100 mg every 12 h), oral rifampin (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 or 160/800 every 12 h). In neurobrucellosis patients and pregnant women, intravenous ceftriaxone (2 g per day) was added to the regimen initially for 2–4 weeks, and other antimicrobials were given for at least 6 weeks. When required, the duration of therapy was extended and data were recorded.

All patients were followed up for at least 2–3 weeks during hospitalization. Outpatients were called for control visits at 2-week intervals. At the control visits, complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and liver enzymes were examined. In addition, STA was performed after a one-month interval. All patients were followed up for at least 6 weeks after completing therapy. After the treatment period, patients were recalled for the first control visit two weeks later and then at 6, 10 and 14 weeks, 6 months, and 1 year later. At the first control visit, complete blood count, CRP, ESR, and liver enzymes were examined and STA performed. These tests were repeated at each further control visit until full recovery. During the follow-up period, blood cultures were only performed in those cases that were assumed to be relapsed cases.

Results

Of the total 1028 patients, 539 (52.4%) were female and 489 (47.6%) were male. The mean patient age was 33.7 $\pm$ 16.34 years, ranging from 3 to 81 years; 36 (3.5%) were aged 3–12 years, while 298 (29.0%) were aged 13–24 years, 251 (24.4%) were aged 25–34 years, 166 (16.1%) were aged 35–44 years, 125 (12.2%) were aged 45–54 years, 131 (12.7%) were aged 55–67 years, and 21 (2.0%) were over 67 years of age.

Of the cases, 435 (42.3%) had a history of raising livestock, while 26 (2.5%) had other occupations carrying a risk for brucellosis (13

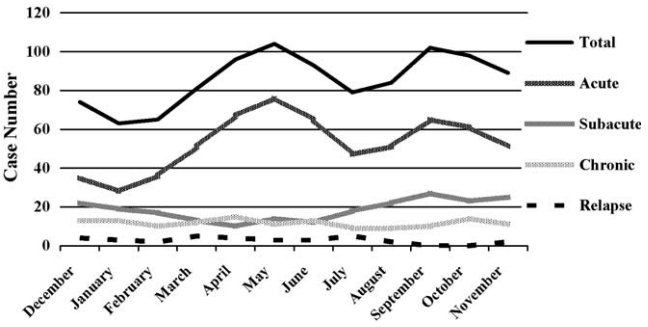

Figure 1. Seasonal distribution of cases.

veterinarians or veterinary technicians, nine butchers or butchery workers, and four laboratory technicians). Of the cases, 55.2% were found to have no occupational risk for brucellosis. Six hundred and fifty-four of the cases (63.6%) had a history of consumption of raw milk and dairy products. There was a family history of brucellosis in 17.8% of the cases. Thirty-one (3.0%) cases had none of the risk factors for brucellosis.

With regard to clinical findings, 633 (61.6%) cases were evaluated as acute, 222 (21.6%) as subacute, and 140 (13.6%) as chronic, while 33 (3.2%) were evaluated as relapse cases. In terms of gender distribution, 333 acute cases (52.6%), 117 subacute cases (52.7%), 71 chronic cases (50.7%), and 18 relapse cases (54.5%) were female.

The seasonal distribution of cases is shown in Figure 1. While acute cases were seen intensively in spring (30.6%), subacute cases were mainly seen in the autumn (33.8%). There were peaks for acute cases in May and September.

The most frequent symptoms were arthralgia (73.7%), fever (72.2%), and fatigue (71.2%). The most frequent clinical findings were fever (28.8%), hepatomegaly (20.6%), splenomegaly (14.5%), and peripheral arthritis (14.3%) (Table 1).

In a comparison of those in the 3–14 years age group and adults, most of the cases (89.7%) were acute and subacute. There were fewer chronic cases in children (four cases) than in adults (5.1% vs. 14.3%), however the numbers of relapsing cases (four cases) were similar (5.1% vs. 3.1%). The seasonal distribution of acute and subacute cases was similar in both groups. In children, the most frequent symptoms were arthralgia (85.9%), fever (71.8%), fatigue (55.1%), sweating (50%), loss of appetite (37.2%), and weight loss (35.9%). Abdominal pain occurred more frequently than in the adult group (25.6% vs. 6.7%), while myalgia occurred less frequently (17.9% vs. 36.1%). The most frequent clinical and laboratory findings in children were anemia (47.4%), fever (28.2%), peripheral arthritis (21.8%), hepatomegaly (17.9%), leukopenia (15.4%), and splenomegaly (14.1%). Peripheral arthritis occurred more frequently than in the adult group (21.4% vs. 14.3%), while sacroiliitis was less frequent (2.6% vs. 6.2%) and spondylitis was not seen.

The most common laboratory findings were high CRP levels (58.4%), high ESR (51.3%), and anemia (40.3%). The STA test was positive in 967 (94.1%) cases, with titers ranging from 1/160 to 1/163 840. Forty-nine cases (4.8%) who had a negative STA were found to be positive by Coombs STA. Twelve cases (1.2%) were seronegative; six of these showed *Brucella spp* growth in their cultures and the remaining six were diagnosed following a good response to anti-Brucella therapy (clinical and laboratory findings, especially ESR and CRP improved). These cases remained seronegative on at least three occasions during the follow-up period; they were then lost to follow-up.

Table 1
Symptoms and findings of the cases according to clinical type

	Acute brucellosis ($N=633$)		Subacute brucellosis ($N=222$)		Chronic brucellosis ($N=140$)		Relapse brucellosis ($N=33$)		Total brucellosis ($N=1028$)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Symptom										
Arthralgia	472	74.5	167	75.2	94	67.1	25	75.8	758	73.7
Fever	487	76.9	146	65.7	90	64.3	19	57.6	742	72.2
Fatigue	457	72.2	164	73.9	87	62.1	24	72.7	732	71.2
Sweating	425	67.1	141	63.5	79	56.4	21	63.6	666	64.8
Lack of appetite	331	52.3	108	48.6	48	34.3	17	51.5	504	49.0
Weight loss	268	42.3	103	46.4	53	37.9	12	36.4	436	42.4
Myalgia	238	37.6	105	47.3	18	12.9	10	30.3	371	36.1
Chills	292	46.1	48	21.6	0	0	8	24.2	348	33.9
Upper back pain	52	8.2	13	5.9	3	2.1	2	6.1	70	6.8
Lower back pain	146	23.1	39	17.6	27	19.3	6	18.2	218	21.2
Nausea/vomiting	167	26.4	63	28.4	18	12.9	8	24.2	256	24.9
Abdominal pain	48	7.6	15	6.8	5	3.6	1	3.0	69	6.7
Headache	119	18.8	22	9.9	5	3.6	2	6.1	148	14.4
Cough	17	2.7	4	1.8	0	0	0	0	21	2.0
Epistaxis	8	1.3	0	0	0	0	0	0	8	0.8
Scrotal pain	24	3.8	10	4.5	1	0.7	0	0	35	3.4
Findings										
Fever[a]	233	36.8	58	26.1	0	0	5	15.2	296	28.8
Hepatomegaly	142	22.4	47	21.2	19	13.6	4	12.1	212	20.6
Splenomegaly	102	16.1	29	13.1	15	10.7	3	9.1	149	14.5
Hepatosplenomegaly	79	12.5	16	7.2	10	7.1	1	3.0	106	10.3
Lymphadenopathy	15	2.4	6	2.7	4	2.9	0	0	25	2.4
Stiff neck	43	6.8	8	3.6	0	0	0	0	51	5.0
Peripheral arthritis	93	14.7	39	17.6	12	8.6	3	9.1	147	14.3
Spondylitis	8	1.3	12	5.4	12	8.6	0	0	32	3.1
Sacroiliitis	32	5.1	19	8.6	7	5	6	18.2	64	6.2
Endocarditis	5	0.8	2	0.9	0	0	0	0	7	0.7
Skin lesion	15	2.4	7	3.2	3	2.1	0	0	25	2.4
Icterus[b]	14	2.2	1	0.5	0	0	1	3.0	16	1.6
Scrotal swelling	24	3.8	10	4.5	1	0.7	0	0	35	3.4

[a] Fever: $\geq$38 °C.
[b] Icterus: total bilirubin $\geq$2.5 mg/dl.

Table 2
Laboratory findings of the cases according to clinical type

	Acute brucellosis (*N* = 633)		Subacute brucellosis (*N* = 222)		Chronic brucellosis (*N* = 140)		Relapse brucellosis (*N* = 33)		Total brucellosis (*N* = 1028)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Non-specific laboratory findings										
Anemia[a]	278	43.9	88	39.6	39	27.9	9	27.3	414	40.3
Leukopenia[b]	97	15.3	13	5.9	1	0.7	1	3.0	112	10.9
Leukocytosis[b]	60	9.5	19	8.6	10	7.1	4	12.1	93	9.0
Thrombocytopenia[c]	75	11.8	14	6.3	6	4.3	3	9.1	98	9.5
Pancytopenia	44	7.0	4	1.8	1	0.7	1	3.0	50	4.9
Lymphomonocytosis[d]	165	26.1	74	33.3	43	30.7	8	24.2	290	28.2
ESR 20–40 mm/h	182	28.8	81	36.5	46	32.9	17	51.5	326	31.7
ESR >40 mm/h	129	20.4	38	17.1	31	22.1	3	9.1	201	19.6
Transaminase elevation[e]	198	31.3	36	16.2	18	12.9	3	9.1	255	24.8
Bilirubin elevation[f]	66	10.4	6	2.7	0	0	2	6.1	74	7.2
CRP positive	417	65.9	117	52.7	48	34.3	18	54.5	600	58.4
RF positive	22	3.5	6	2.7	7	5	4	12.1	39	3.8
Specific laboratory findings										
STA positive	601	94.9	199	89.6	134	95.7	33	100	967	94.1
Coombs STA positive	26	4.1	19	8.6	4	2.9	0	0	49	4.8
Seronegative cases	6	0.9	4	1.8	2	1.4	0	0	12	1.2
Culture positive/culture taken cases	125/284	44.0	32/87	36.8	5/18	27.8	1/7	14.3	163/396	41.2
Culture positive/all cases	125/633	19.7	32/222	14.4	5/140	3.6	1/33	3.0	163/1028	15.9
Blood	95	15.0	19	8.6	2	1.4	1	3.0	117	11.4
Bone marrow	16	2.5	8	3.6	2	1.4	0	0	26	2.5
Other	14	2.2	5	2.3	1	0.7	0	0	20	1.9

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; STA, standard tube agglutination.
[a] Anemia: female ≤12 g/dl and male ≤13.5 g/dl.
[b] Leukopenia: $<4 \times 10^9$/l; leukocytosis: $>11 \times 10^9$/l.
[c] Thrombocytopenia: $<150 \times 10^9$/l.
[d] Relative lymphomonocytosis.
[e] Alanine aminotransferase (ALT): ≥50 IU/l and aspartate aminotransferase (AST): ≥50 IU/l.
[f] Bilirubin elevation: total bilirubin ≥1.5 mg/dl.

Table 3
Focal involvement of the cases according to clinical type

Involvement type	Acute brucellosis (*N* = 633)		Subacute brucellosis (*N* = 222)		Chronic brucellosis (*N* = 140)		Relapse brucellosis (*N* = 33)		Total brucellosis (*N* = 1028)	
	n	%	*n*	%	*n*	*n*	%	*n*	%	*n*
Osteoarticular	138	21.8	77	34.7	36	25.7	9	27.3	260	25.3
CNS	49	7.7	8	3.6	1	0.7	0	0	58	5.6
Epididymo-orchitis	24	3.8	10	4.5	1	0.7	0	0	35	3.4
Liver	23	3.6	4	1.8	0	0	1	3.0	28	2.7
Skin	15	2.4	7	3.2	3	2.1	0	0	25	2.4
Hematologic	13	2.1	4	1.8	0	0	0	0	17	1.7
Cardiovascular	5	0.8	2	0.9	0	0	0	0	7	0.7
Pleurisy	5	0.8	2	0.9	0	0	0	0	7	0.7
Peritonitis	2	0.3	3	1.4	0	0	0	0	5	0.5
Soft tissue	2	0.3	1	0.5	0	0	0	0	3	0.3
Kidney	2	0.3	0	0	0	0	0	0	2	0.2
Retinitis	1	0.16	0	0	0	0	0	0	1	0.1
Thyroiditis	1	0.16	0	0	0	0	0	0	1	0.1
Prostatitis	1	0.16	0	0	0	0	0	0	1	0.1
Pancreatitis	1	0.16	0	0	0	0	0	0	1	0.1
Patients with focal involvement	225	35.5	97	43.7	40	28.6	9	27.3	371	36.1

CNS, central nervous system.
Some of the patients had more than one focal involvement.

Brucella growth was achieved in 163 of 396 cases from whom appropriate cultures were taken. Of these, 117 were from blood (71.8%), 26 from bone marrow (16.0%), three from CSF (1.8%), eight from joint fluid (4.9%), four from abscess material (2.5%), three from paracentesis fluid (1.8%), one from thoracentesis fluid (0.6%), and one from ejaculate (0.6%). Isolation was achieved from 117 of 298 blood cultures (39.3%), 26 of 47 bone marrow cultures (55.3%), and 20 of 51 cultures from other sites (39.2%). The lowest growth rate was seen in CSF with 10.7%. Typing was possible for only 83 isolates, yielding *Brucella melitensis*. Table 2 summarizes the laboratory findings of the cases.

Focal involvement was present in 371 (36.1%) cases (Table 3). The most frequent involvement was osteoarticular involvement with 260 cases (25.3%). Osteoarticular involvement included peripheral arthritis (56.5%), sacroiliitis (24.6%), spondylitis (12.3%), and paraspinal abscess (3.5%). Monoarthritis was seen in 50 patients, while polyarthritis was found in 97 cases. Sacroiliitis was unilateral in 51 and bilateral in 13 cases.

Laboratory abnormalities with regard to the hematologic system were present in 452 cases (44.0%), but the rate of clinically affected patients was much lower at 1.7% (seven cases with petechiae and purpura, six cases with epistaxis, two cases with

Table 4
Initial therapeutic regimens, follow-up patients, and results according to patient groups

Treatment regimens according patients	Number of cases	Follow-up patients	Relapse, *n* (%)
Osteoarticular involvement[a]	255[b]	141	12 (8.5)
Doxycycline + rifampin	62	35	4 (11.4)
Doxycycline + streptomycin[c]	81	41	3 (7.3)
Doxycycline + rifampin + streptomycin[c]	95	53	3 (5.7)
Ciprofloxacin + doxycycline or rifampin	17	12	2 (16.7)
Neurobrucellosis[d]	58	49	–
Doxycycline + rifampin + ceftriaxone[e]	39	34	–
Rifampin + Doxycycline + co-trimoxazole	9	7	–
Rifampin + Doxycycline + streptomycin[c]	10	8	–
Other patients[f]	715	346	13 (3.8)
Doxycycline + rifampin	193	72	3 (4.2)
Doxycycline + streptomycin[c]	137	57	2 (3.5)
Doxycycline + rifampin + streptomycin[c]	103	61	2 (3.3)
Doxycycline + rifampin + levamisole[g]	72[h]	43	1 (2.3)
Doxycycline + rifampin + streptomycin[c] + levamisole[g]	53[h]	36	–
Doxycycline + ciprofloxacin	44	22	1 (4.5)
Rifampin + co-trimoxazole	33	15	–
Rifampin + ciprofloxacin	27	11	1 (9.1)
Other regimen[i]	53	29	3 (10.3)

[a] Treatment duration 6–12 weeks.
[b] Pregnant women and patients under 8 years of age excluded.
[c] For 4–21 days.
[d] Treatment duration 12–24 weeks.
[e] For 21–30 days.
[f] Treatment duration 6–12 weeks.
[g] For 6 weeks, 80 mg every other day.
[h] Only chronic cases and treatment duration 12–24 weeks.
[i] For pregnant women and children <8 years of age.

both petechiae and epistaxis, one case with DIC and one case with thrombophlebitis).

Central nervous system (CNS) involvement was present in 58 cases (5.6%). Of these, seven had encephalitis (12.1%), two had myelitis (3.4%), two had polyradiculoneuritis (3.4%), one had a hypophysis abscess (1.7%), and one had a frontal abscess (1.7%). The remaining 45 patients had either meningitis or meningoencephalitis (77.6%). Four patients had toxic febrile neurobrucellosis and one had status epilepticus.

Genitourinary system involvement was present in 38 (3.7%) patients, mainly presenting as epididymo-orchitis with 35 cases (3.4%), being bilateral in three cases. Three of the unilateral cases required orchiectomy because of testicular abscess formation. One patient had prostatitis, and *Brucella spp* were isolated from semen. In terms of renal involvement, we detected one patient with tubulo-interstitial nephritis and one with glomerulonephritis and endocarditis at the same time. Seventeen of our cases were pregnant (1.7%). None of them had a miscarriage or abortion during follow-up.

Elevated transaminase levels were detected in 24.8%, while hepatic involvement was present in only 28 patients (2.7%). Twenty-five patients (2.4%) had skin involvement; 13 had a maculopapular-urticarial rash, nine had petechiae–purpura, and three had erythema nodosum. Seven patients had cardiovascular involvement (0.7%), all with endocarditis. One of the patients had renal failure, followed by a secondary infection and later died, while another died because of chordae tendineae rupture with acute cardiac failure. Three patients were lost to follow-up and two others underwent cardiac surgery. Two patients died because of endocarditis and the third died because of neurobrucellosis with delayed admission to hospital.

Various initial regimens were administered to the 1028 patients with brucellosis. Only 536 patients were followed up for one year. The treatment regimens and relapse rates are given in Table 4. Ceftriaxone and co-trimoxazole were added to the regimen of patients diagnosed with neurobrucellosis or in the case of pregnancy. Patients having no nervous system or osteoarticular involvement were given various regimens. The treatment duration was 6–12 weeks in osteoarticular involvement, 12–24 weeks in neurobrucellosis, and 6–12 weeks for the other clinical forms. In chronic patients, levamisole was added (6 weeks, 80 mg every other day) and the treatment duration was extended to 12–24 weeks. The overall relapse rate in patients with brucellosis was 4.7%. The relapse rate in patients with osteoarticular involvement was higher than that of patients with other involvements (8.5% vs. 3.7%).

Discussion

Brucellosis is the most frequent zoonotic infectious disease in the world, affecting more than 500 000 people each year.[5] The first systematic study of the epidemiology of brucellosis in Turkish patients was performed by Çetin et al. between 1984 and 1987. In this multicenter study, more than 70 000 subjects were investigated for Brucella seropositivity, revealing 6% seropositivity in the high-risk population and 1.8% in the entire study population.[14] Among high-risk patients in the eastern part of Turkey, seropositivity has been reported to be as high as 27.2%.[15] However, the true rates of brucellosis in endemic countries are most probably higher than reported due to deficiencies in its diagnosis or recording.[16]

In endemic countries, brucellosis is more prevalent in the 15–35 years age group.[1,2] In the present study 53.4% of patients were between 13 and 34 years of age. Some epidemiological studies from Turkey have reported relatively younger ages compared to studies from outside Turkey. This may be attributed to involvement in the raising of livestock starting at a younger age in our country.[17,18] On the other hand, some studies from Turkey and outside Turkey have reported higher mean ages.[13,19–22] In a recent study by Gül et al. from Turkey, a mean age of 27 ± 3.6 years was reported in a population comprising 80.7% male and 19.3% female.[23] The differences between these results could be explained by the diversity of populations, because the latter study was performed in a military hospital.

Brucellosis may appear in four different forms, namely acute, subacute, chronic, and relapse.[1–3] In our study, the acute

Table 5
Comparison of gender, age, and clinical types of brucellosis in various studies

Author [Ref.]	Country	No. of cases	Female %	Male %	Mean age, years	Acute brucellosis (%)	Subacute brucellosis (%)	Chronic brucellosis (%)
Akdeniz et al. [24]	Turkey	233	54	46	29.1[a]; 35.2[b]	58.3	14.2	27.5
Aygen et al. [20][c]	Turkey	480	55.2	44.8	44.1 ± 16.4	67.1	25.2	5
Gür et al. [17]	Turkey	283	49	51	32.69 ± 14.39	25	59	16
Kökoğlu et al. [25]	Turkey	138	48.5	51.5	32.2 ± 14.1	57.2	16.7	26.1
Savaş et al. [21]	Turkey	140	72.9	27.1	45.81 ± 15.62	53.6	21.4	25
Demiroğlu et al. [22]	Turkey	151	58.9	41.1	45.4 ± 16	66.2	23.9	9.9
Roushan et al. [19]	Iran	469	43.1	56.9	36.97 ± 15	54.4	38.2	7.4
Lulu et al. [36]	Kuwait	400	37	63	33	77	12.5	10.5
Mantur et al. [39]	India	495	21.2	78.8	31[d]	62.6	29.5	7.9
Present study	Turkey	1028	52.4	47.8	33.70 ± 16.34	61.6	21.6	13.6

[a] Male.
[b] Female.
[c] Asymptomatic patients 2.7%.
[d] Accounted for 390 of the cases.

presentation constituted most of the cases (61.6%), whereas subacute and chronic cases constituted 21.6% and 13.6% of the cases, respectively; this is in accordance with previous reports (Table 5). Although Akdeniz et al.[24] have reported a higher rate (27.5%) in our region, the chronic infection rate of 13.6% in our study is higher than that of some previous reports, which can be explained by treatment failure or hyperendemicity in our region. However, certain studies have also reported higher incidences of chronic or subacute infections.[17,21,25]

The primary transmission route of brucellosis is by the ingestion of unpasteurized dairy products in endemic countries, whereas in developed countries infection occurs mostly due to occupational exposure.[1–3] In our geographic region – the Lake Van basin – the most common route of spread is the consumption of regional herbaceous cheese produced from raw milk.[15,24,26] A history of raw dairy product consumption was present in 63.6% of the cases in our study. In some epidemiologic studies from Turkey, a history of raw dairy product consumption has been reported for between 62.6% and 94.6% of cases.[17,18,22,27–29] The consumption of raw dairy products in other studies has been reported as occurring in 23.6% of cases in Spain by Colmenero et al.,[13] 69% in Kuwait by Mousa et al.,[30] 34.7% in the Balkan Peninsula by Bosilkovski et al.,[31] and 22.4% in Iran by Roushan et al.[19] A history of a local traditional food – raw meat ball – consumption was reported in 55% in the series of Gür et al.[17] and 57% in Kılıç et al.[32]

In developed countries, most of the brucellosis cases occur due to occupational exposure. High-risk occupations for the disease are the raising of livestock, butchery, farming, and veterinary

Table 6
Comparison of symptoms and signs in various studies

	Author [Ref.]							
	Akdeniz et al. [24]	Kökoğlu et al. [25]	Aygen et al. [20]	Memish et al. [38]	Mantur et al. [39]	Mousa et al. [30]	Colmenero et al. [13]	Present study
Country	Turkey	Turkey	Turkey	Saudi Arabia	India	Kuwait	Spain	Turkey
Number of cases	233	138	480	160	495	379	530	1028
Symptoms %								
Fever	73	78.3	79.8	91		90.5		72.2
Sweating		72.5	84.4	19[a]	3.8	38.8	84.9	64.8
Fatigue	71	71	90		1.2		73[b]	71.2
Lack of appetite	50	57.2	41.3			25		49
Chills		44.2		49		38.7	86	33.9
Arthralgia	68	77.5	81.9	66	23.6	21.1	50.1	73.7
Nausea/vomiting	15	16.7/8.7	32.3/21.7		2.6	-/15		24.9
Headache	12	51.4	19	16	1.6	22.2		14.4
Lower back pain					17.9		23.6	21.1
Upper back pain			58.5			14.8		6.8
Abdominal pain	22	15.9	21		2.6	7		6.7
Myalgia	57	50.8	49.2			21.4	38.7	36.1
Weight loss	54		44.4			7		42.4
Testicular pain					2.8		4.5	3.4
Signs %								
Fever		40.6	39	84	84.2		98.1	28.8
Splenomegaly	22	36.2	14.2	7	29	42.2	22.3	24.8
Hepatomegaly	34	26.8	21.3	6	21.1	36.9	38.1	30.9
Lymphadenopathy	6	9.4			2.4	8.7	9.1	2.4
Osteoarticular involvement	21	46.4	19	43		36.9	23	25.3
CNS involvement/stiff neck	2	3.6	6.5	5	1.4		9.1[c]	5
Endocarditis/cardiovascular involvement	1	1.5	0.4	2	1.2			0.7
Skin lesion/rash	2	8.7	0.4		1		3.4	2.4
Peritonitis			0.4					0.5
Epididymo-orchitis/prostatitis/ genitourinary system involvement	5	7.5	1	2	2.2	22		3.7

[a] Excessive sweating.
[b] Constitutional symptoms: at least two of asthenia, lack of appetite, and fatigue.
[c] Neurological sign.

medicine. Laboratory transmission has also been reported.[1,2] In studies from Turkey, a history of livestock raising has been shown for between 14.6% and 70.3% of cases,[17,18,21,22,27,33–35] whereas a history of livestock raising in other countries has been reported in 11.1% from Kuwait by Mousa et al.,[30] 9% also from Kuwait by Lulu et al.,[36] 11.3% from Iran by Roushan et al.,[19] and 20% from Greece by Andriopoulos et al.[37] In our population, raising livestock was evident for 42.3% of patients, which is in accordance with previous reports from Turkey. Demirtürk et al. reported 41.1% non-occupational and 3% occupational contact with an animal.[29] However in our region, most of the families, particularly housewives, deal with the raising of livestock, which increases the contact rate in our study. Occupational contact was found in 26 patients in our study (2.5%; 13 veterinarians, nine slaughterhouse workers, and four laboratory technicians). No contact history was identified in 55.2% of patients. In previous reports, a family history of brucellosis has been reported for between 12.6% and 43% of cases in Turkey,[17,22,27,35] and also in 9.6% in the study by Roushan et al.[19] from Iran. In our study, a family history was present in 17.8% of patients. This may be attributed to the concept of a larger family in our region. In our study, 31 patients (3%) had no risk factor for brucellosis. Risk factors in other studies have been found for between 10.9% and 28.7% of cases,[13,17,18,30,31] and even higher rates have been reported (41.8% by Yüce et al.[35] and 56.7% by Roushan et al.[19]).

Most brucellosis cases present in the spring and summer months.[1–3] Gür et al reported that 68% of cases presented in the spring and summer.[17] Savas et al. observed the highest presentation in July and the lowest in January in their study.[21] Lulu et al.[36] reported that 78% of the cases were seen in the March–July period, peaking in April–May. Roushan et al.[19] reported that 25.2% of cases occurred in spring, 40.1% in summer, 22% in autumn, and 12.8% in winter months. In our study, 30.6% of acute cases presented in the spring, whereas 33.8% of subacute cases presented in the autumn. No seasonal difference was observed for chronic and relapsed cases. Two peaks were observed in our study, the first in April–May, which could be due to the increased use of fresh cheese, and the second in September, which could be due to the use of stored cheese from the spring season. Similarly two previous studies from the same region performed by Akdeniz et al.[24] and Gür et al.,[17] have reported a second peak in September.

Typically acute brucellosis cases present with chills, fever, fatigue, sweating, weight loss, and back pain.[1,2] Subacute cases show a protean clinical presentation, although with less severe symptoms compared to the acute form. Patients with the chronic form of the disease usually present with complaints of malaise, nervousness, emotional lability, depression, or generalized musculoskeletal pain.[2,3] In our study population, most of the patients complained of arthralgia, fever, and fatigue. In acute cases, fever was observed in 76.9% of patients, arthralgia in 74.5%, and fatigue in 72.2% of the patients. In subacute cases, arthralgia was reported in 75.2% of the patients, and fatigue and fever were reported in 73.9% and 65.7% cases, respectively. In the chronic form, 67.1% of cases had arthralgia, 64.3% had fever, and 62.1% had fatigue. In relapsed cases, arthralgia was evident in 75.8% of cases; fatigue, sweating, and fever were evident in 72.7%, 63.6% and 57.6% of cases, respectively.

In our study, 72.2% of patients complained of fever, but it was only evident as a clinical finding in 28.8%. These results are in accordance with two previous studies, which reported fever as a symptom in 78.3% but as a sign in 40.6% (Kokoglu et al.[25]) and as a symptom in 79.8% vs. as a sign in 39% (Aygen et al.[20]). The studies that reported a higher rate of fever as a clinical finding in brucellosis are available in the literature.[13,38,39] This difference could be due to the administration of over-the-counter non-steroidal anti-inflammatory drugs for relieving musculoskeletal pain. The typical undulant fever was observed rarely and most patients with undulant fever were either late presentation or untreated cases. A brief review of brucellosis symptoms obtained from large epidemiologic studies is presented in Table 6.

Anemia, leukopenia, thrombocytopenia, elevated liver enzymes, and increased CRP were the most prominent laboratory abnormalities seen in acute and subacute cases. Increased ESR and lymphomonocytosis were observed to the same extent in all forms. Rheumatoid factor was found positive only in chronic cases and relapses.[1–3]

Serology is the preferred method for the diagnosis of brucellosis when bacterial isolation is not possible, and serologic testing is widely used in the diagnosis of brucellosis.[1–3] STA test positivity was reported in 95% by Akdeniz et al.[24] and in 87% by Taşova et al.[18] The STA test was positive in 94.1% of our study population. Coombs STA test is preferred when the STA test is found negative. Coombs STA test was positive in 4.8% of cases in our study, in accordance with the previous report by Akdeniz et al. with 5%.[24] Following these tests, 1.1% of our patients remained seronegative. Demiroğlu et al. also reported 1.3% seronegativity in their study.[22]

In regions endemic for brucellosis such as ours, serological test results should only be interpreted as significant in the presence of clinical findings compatible with brucellosis, and in suspect cases, treatment should be delayed until various serologic tests have been performed (Coombs test, 2-mercaptoethanol (2-ME) agglutination test, Brucellacapt, ELISA) during the follow-up of the cases.

A definite diagnosis of brucellosis relies on isolation of the bacteria from blood, bone marrow, or from other tissue cultures. The reported bacterial isolation rates in the literature range from 15% to 90% depending on the methodology used.[1,2] Previous antibiotic use significantly decreases the likelihood of bacterial isolation in blood cultures in chronic cases.[20,40] Bone marrow cultures may provide a higher sensitivity, yield faster culture times, and may be superior to blood cultures when evaluating patients with previous antibiotic use.[41,42] In our study, culture positivity was higher in acute cases (44.0%) than in the other forms. Isolation of bacteria from bone marrow was achieved in 55.3% of patients, but CSF had the lowest isolation rate (10.7%). A brief summary of laboratory abnormalities reported in other epidemiologic studies is presented in Table 7.

Brucella infection may involve any organ or tissue in the body. Organ involvement can be assigned as focal involvement or as a complication. The most common systems affected are the locomotor, gastrointestinal, genitourinary, hematologic, cardiovascular, respiratory, and central nervous systems.[1,2] Focal involvement rates of between 27.7% and 43.2% have been reported.[13,20,33,35] In our study, focal involvement was observed in 36.1% of cases. Focal involvement characteristics in the large epidemiologic studies are reviewed in Table 8.

Osteoarticular involvement occurs in 20–85% of cases.[1,2] Osteoarticular involvement rates of between 58.8% and 79.5% have been reported,[17,22,43,44] but lower rates of between 9.3% and 22.8% have also been reported.[20,45–48] In our study, osteoarticular involvement was observed in 21.8% of acute cases, 34.7% of subacute cases, 25.7% of chronic cases, and in 27.3% of relapsed cases, with an overall rate of 25.3%, similar to that found by Akdeniz et al.[24] (21% of the total cases). The enormous range between reports in the literature may be due to characteristics of the study populations, the radio-diagnostic methods used, and the different diagnostic criteria employed. The rate of osteoarticular involvement in children was 24.4%, similar to the rate in adults, but most of them presented as peripheral monoarthritis.

As the largest organ of the reticuloendothelial system, the liver is affected in almost all patients with brucellosis. Liver involvement results in mild to moderate elevation in liver enzymes.[1,2] On the other hand, all cases with elevated liver enzymes should not be

Table 7
Comparison of laboratory findings in various studies

	Author [Ref.]						
	Akdeniz et al. [24]	Aygen et al. [20]	Demiroğlu et al. [22]	Lulu et al. [36]	Roushan et al. [19]	Colmenero et al. [13]	Present study
Country	Turkey	Turkey	Turkey	Kuwait	Iran	Spain	Turkey
Number of cases	233	480	151	400	469	530	1028
Anemia	55	54.6	51.7	7	15.1	48.1	40.3
Leukopenia	21	7.7	6.6	19	3	28.7[b]	10.9
Leukocytosis		6.5		9	12.2	5.5[c]	9
Thrombocytopenia	26	13.7	2	12	3.4	14.4[e]	9.5
Pancytopenia	8			3.5		6	4.9
Lymphomonocytosis	40	68.3[a]	44.4	41		92.1[f]	28.2
ESR >20 mm/h	61	58.8	61.6	77	77.8	66.8	31.7
ALT/AST elevations (≥50 IU/l)	15		15.2[g]	40/54		49.8/50.6	24.8
CRP positive (>6 mg/l)	36		59.6		59.1		58.4
RF positive	4				8.5		3.8
STA positive (≥1/160)	95		98.7			510	94.1
Coombs STA positive	5						4.8
STA positive (total)		91.7				527	98.9
Seronegative cases			1.3				1.2
Culture positive	53	45	68	30			15.9[d]
Blood	48	41.1	51.2			68.8	11.4[d]
Bone marrow	61	43.5	1				2.5[d]
CSF	20	35.5				1	0.3[d]
Joint fluid		45.5	1			1	0.8[d]
Other		1 case	4 cases			1 case	9 cases

ESR, erythrocyte sedimentation rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; RF, rheumatoid factor; STA, standard tube agglutination; CSF, cerebrospinal fluid.
[a] ≥45%.
[b] $<4.5 \times 10^9$/l.
[c] $>10 \times 10^9$/l.
[d] According to total cases.
[e] $<130 \times 10^9$/l.
[f] $>1 \times 10^9$/l.
[g] ALT >70 IU/l.

evaluated as liver involvement. Hepatic involvement has been reported in the literature in around 2–3%.[13,17,43] Lulu et al. reported 40% hepatic involvement in their study, namely 1% clinical hepatitis and 38.5% anicteric hepatitis.[36] In our study, liver enzyme elevation was observed in 24.8% of the cases and a diagnosis of clinical hepatitis was made in only 2.7% of cases.

Neurobrucellosis occurs in less than 5% of brucellosis patients. Neurological manifestations of the disease are frequently meningitis or meningoencephalitis.[1,2] Although bacterial isolation was not possible in most cases, CNS involvement was reported at between 1.3% and 2%.[13,18,24] In our study, 5.6% of cases were diagnosed with neurobrucellosis, which is consistent with most reports from Turkey and Spain. Among these reports, the Brucella recovery rate has been reported at between 6% and 7% in CSF.[17,20,49,50] This high incidence of neurobrucellosis in our report may be due to referral of this particular group to our clinic, while cases with other organ involvement could be managed at other clinics. The fact that one of our cases died because of neurobrucellosis with delayed admission emphasizes the serious and possibly fatal outcome of the situation and the value of early admission, diagnosis, and treatment in neurobrucellosis.

Urogenital involvement occurs in 2–10% of patients, with unilateral epididymo-orchitis as the most common presentation.[1,2] In our study, 3.4% of patients had epididymo-orchitis, which is in accordance with previous reports.[13,17,22–24,33,43] Epididymo-orchitis was present in 3.8% of acute, in 4.5% of subacute, and in 0.7% of chronic cases. *Brucella spp* grew in the ejaculate of one patient with prostatitis. Colmenero et al.[13]

Table 8
Systems involvement and rates in brucellosis in various studies

Author [Ref.]	Country	No. of cases	Osteoarticular	Hematological	Cardiovascular	Respiratory system	GUS	Skin	Liver	CNS
Aygen et al. [20]	Turkey	480	19		0.4^{end}	1^{pn} case	1^{eo+pr}	0.4		6.5
Gür et al. [17]	Turkey	283	69	$4^{t+pan+ha}$	2^{car} cases	$5^{pn+br+pz}$	$8^{eo+py+pr}$	17^{sr}	3^{h} cases	7
Ertek et al. [43]	Turkey	216	68.1	2.8^{t+pan}	2.3^{end}		5.5^{eo}	4.2^{sr+en}	3.2^{h}	4.2
Örmen et al. [33]	Turkey	104	23		1.9^{end}	6.5^{pn}	3.8^{eo}			0.9
Gül et al. [23]	Turkey	140	41				6^{eo}	3		7
Demiroğlu et al. [22]	Turkey	151	33.7				$5.3^{eo+pr+uti}$	0.7		6
Colmenero et al. [13]	Spain	530	21.3	6^{pan}, 2^{dic} cases	$1.5^{end+my+p}$	1 case	5.1^{eo+pr}	3.8	2.5^{h+la}	1.7
Roushan et al. [19]	Iran	469	28.6		0.6^{end}		6.2^{eo}	2^{en} cases	1^{ih} case	1 case
Mantur et al. [39]	India	495			1.2^{end}	1^{pn+br}	$2.8^{eo+h+uti}$	1^{sr+sjs}		1.4
Barroso Garcia et al. [48]	Spain	890	22.8	$9.9^{ep,*}$	$0.7^{car+phl}$	0.5	6.9^{eo+m}		4.5	4.2
Present study	Turkey	1028	25.3	1.7	0.7	0.7^{pz}	3.4^{eo+pr}, 0.2^{gn}	2.4		5.6

GUS, genitourinary system; CNS, central nervous system.
br, bronchitis; car, carditis; dep, depression; dic, disseminated intravascular coagulation; en, erythema nodosum; end, endocarditis; ep, epistaxis; eo, epididymo-orchitis; gn, glomerulonephritis; h, hepatitis; ha, hemolytic anemia; ih, icteric hepatitis; la, liver abscess; m, mastitis; my, myocarditis; p, pericarditis; pan, pancytopenia; phl, phlebitis; pn, pneumonia; pr, prostatitis; py, pyelonephritis; pz, pleurisy; sjs, Stevens–Johnson syndrome; sl, skin lesion; sr, skin rash; t, thrombocytopenia; uti, urinary tract infection.
[*] In 565 cases.

reported 14 cases of epididymo-orchitis, four cases of prostatitis, and one case with both epididymo-orchitis and prostatitis.

Renal involvement is a rare manifestation of brucellosis. Glomerulonephritis and tubulointerstitial nephritis have been reported in some case reports.[1,2] In our study, one patient presented with tubulo-interstitial nephritis and another with pyelonephritis and endocarditis. The latter case progressed to chronic renal failure and subsequently died. In our opinion, renal involvement may occur more frequently than previously thought in brucellosis, and may be under-diagnosed in nephrology clinics.

Less than 5% of brucellosis patients exhibit non-specific skin symptoms, such as erythema, papules, petechiae, urticaria, impetigo, eczematous rash, erythema nodosum, subcutaneous abscess, and cutaneous vasculitis.[1,2] Skin involvement has been reported in 0.7–17% of cases.[17,22–24,43] In our study, skin involvement was observed in 2.4% of acute, in 3.2% of subacute, and in 2.1% of chronic cases, with an overall rate of 2.4%. The difference among reports could be due to the non-specific nature of skin lesions.

Although hematological involvement is frequent in brucellosis, most of these cases are mild, and serious clinical disease is rare. Ertek et al. reported 2.8% hematological involvement in their study.[43] Disseminated intravascular coagulation was reported in two cases by Colmenero et al.[13] and one case each by Akdeniz et al.[24] and Al-Eissa et al.[51] Additionally Al-Eissa et al. reported four cases of acute hemolysis.[51] Ertek et al.[43] reported 0.9% thrombophlebitis in their series. In our study, hematologic involvement, when taking into account laboratory abnormalities, was observed in 452 patients (44.0%), whereas when taking into consideration clinical findings related to hematological involvement, serious clinical disease was only observed in 17 patients (1.7%). None of the patients had hemolysis in our study, but this is probably because these cases may have been followed up at the hematology clinics.

Endocarditis is the most common presentation of cardiovascular involvement, which is reported in less than 2% of patients.[1,2] Akdeniz et al.[24] reported an incidence rate of 1% in their study. Cardiovascular involvement rates in large epidemiological studies are reported at between 1% and 2.3%.[13,17,24,33,43] In our study, seven patients had endocarditis. Five of them had the acute form and the other two the subacute form of the disease. This low rate (0.7%) may be as a result of patients being followed up at the cardiology clinic at the same time.

Despite treatment including several antibiotic regimens, relapse is estimated to occur in 5–40% of patients with acute brucellosis in the following year, depending on antibiotic use, duration of treatment, and drug combination.[52] In this study, the patients were given various regimens. The treatment duration was based on organ involvement, CRP and ESR normalization. The relapse rate of all patients with brucellosis was 4.7%. The highest relapse rate, 8.5%, was observed in the group of patients with osteoarticular involvement.

The doxycycline plus streptomycin regimen could prove to be more effective than the doxycycline plus rifampin regimen in patients with spondylitis.[53,54] In our study, the doxycycline plus streptomycin regimen and the doxycycline plus rifampin plus streptomycin regimen were evaluated to be more effective than other regimens in osteoarticular involvement.

There are no specific guidelines regarding the antibiotic regimens and duration of treatment for neurobrucellosis. Most authorities recommend the use of doxycycline in combination with two or more other drugs, with treatment continued for several months depending on the response. Drugs such as doxycycline, rifampin, and co-trimoxazole have been found to be effective due to their good CNS penetration and synergistic actions.[1] Third-generation cephalosporins diffusing into the CSF, ceftriaxone, ceftizoxime, and cefotaxime have good in vitro activity on clinical isolates of *B. melitensis*.[55] In our opinion, a third-generation cephalosporin in the initial treatment of neurobrucellosis is essential in view of the treatment efficacy, as reported by Aygen et al.[20,56] No relapse case occurred in our 34 patients treated with triple combinations including ceftriaxone.

There is no standard therapy protocol in chronic brucellosis. Although streptomycin, doxycycline, rifampin, and other antibiotic combinations in conjunction with levamisole were used for various durations, a definite treatment protocol has not been recommended.[57] In our study, levamisole was added for 6 weeks (80 mg every other day) and the treatment duration extended to 12–24 weeks in chronic patients. This combination with extended treatment duration appears to be successful in chronic patients.

Brucellosis is an important health problem in Turkey. The disease has a significant morbidity and mortality. Additionally, since the disease primarily affects persons in their productive age, it causes important work-power losses. Eradication of the disease in humans can only be achieved by the control of the disease in animals; this necessitates a multidisciplinary approach involving both humans and animals. In addition to isolation and serological tests, non-specific tests such as CRP and ESR should also be used in treatment follow-up. There is no recommended treatment protocol for complicated brucellosis. Large multicenter studies are needed to determine the most appropriate treatment choices and durations in complicated brucellosis.

Conflict of interest: No conflict of interest to declare.

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