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Complications of Brucellosis in Different Age Groups: A Study of 283 Cases in Southeastern Anatolia of Turkey

Ali Gür[1], Mehmet Faruk Geyik[2], Bunyamin Dikici[3], Kemal Nas[4], Remzi Çevik[4], Jale Saraç[5], and Salih Hosoglu[2]

[1]Department of Physical Therapy and Rehabilitation, Dicle University Medical Faculty, Diyarbakir, Turkey;
[2]Professor, Department of Clinical Microbiology and Infectious Diseases, Dicle University Medical Faculty, Diyarbakir, Turkey;
[3]Professor, Department of Pediatrics, Dicle University Medical Faculty, Diyarbakir, Turkey;
[4]Professor, Department of Physical Therapy and Rehabilitation, Dicle University Medical Faculty, Diyarbakir, Turkey;
[5]Department of Physical Therapy and Rehabilitation, Dicle University Medical Faculty, Diyarbakir, Turkey.

We carried out a retrospective analysis of 283 patients diagnosed with brucellosis in our hospital, which serves almost 5.5 million inhabitants in Southeastern Anatolia in Turkey.

Our study focuses on the frequency of complications in cases with brucellosis across different age groups. Patients were classified into three groups according to age: less than 15 years old (group A), 15-45 years old (group B) and over 45 years old (group C).

Of 283 patients, 138 (49%) were female and 145 (51%) male. Fifty-three (19%) were younger than 15 years old (group A), 178 (63%) were 15-45 (group B), and 52 (18%) were over 45 (group C). When the distribution of all cases was examined according to months of the year, an increase was seen in June. Osteoarticular complications were the most frequent, found in 195 (69%) cases, followed by cutaneous (17%), genitourinary (8%), nervous (7%), respiratory (5%) and hematological (4%) complications. Treatment failed in 15 patients (5%), owing to true relapse in ten and to non-compliance and drug side effects in the other five. Two hundred seventy-two patients received medical treatment alone and 11 required medical and surgical treatment as well (9 spondylitis and 2 carditis). Complications in brucellosis were frequent because 25% of all patients with brucellosis had more than one complication, more so in group C (38%) than in group A (28%) or B (20%). Cutaneous, hematological and respiratory complications in childhood; osteoarticular and cardiac complications in adults; and genitourinary, neurological and gastrointestinal complications in middle aged were more prominent.

In conclusion, the frequency of brucella complications was variable in different age groups in Southeastern Anatolia of Turkey. Since brucellosis is a preventable disease, knowledge and early diagnosis of the complications are especially important. Therefore, population education and medical precautions are necessary to prevent the harmful effects of brucella and its complications. In addition, primary health care physicians should be alerted regarding the clinical and laboratory findings of brucella complications.

Key Words: Brucellosis, clinical symptoms, complications, seasonal distribution, treatment

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Reprint address: requests to Dr. Ali Gür, Physical Medicine and Rehabilitation, Dicle University Medical Faculty, Diyarbakir, Turkey. Tel: 90 412 2488001 (4572), Fax: 90 412 2488440, E-mail: alig@dicle.edu.tr

INTRODUCTION

Brucellosis is a systemic infectious disease. The incidence of the disease in Turkey is 0.59 per 100.000 per annum and there are 500,000 new cases of brucellosis reported annually worldwide. This important health issue sometimes leads to epidemics in the southeastern region in Turkey.[1] Due to its high degree of morbidity, both for animals and humans, it is an important cause of economic loss and represents a serious public health problem in many developing countries.[2-4]

This disease typically attacks the young and middle aged adults, with a low incidence among infants and elderly patients.[5-7] Over the course of time the immune system suffers a gradual involution process leading to significant changes in cellular and humoral immunity among elderly subjects.[8] It may therefore be reasonable to think that the clinical course and outcome of brucellosis in the elderly could be different from those in young patients.

The clinical features of brucellosis are not

disease specific, and almost every organ can be affected. The infection spreads hematogenously to tissues, rich in elements of the reticuloendothelial system, including the liver, bone marrow, lymph nodes and spleen. It may also localize in other tissues including joints, the central nervous system, the heart and the kidneys.[9]

The prevalence and pattern of complications depend on the strain of brucella infecting the individual, the age of the patient, and the duration of the disease.[10-15] Therefore, studies of large populations, with different age groups are very important. Although there are many reports on brucellosis in adults or childhood,[10-12,15,16] as far as we know no comprehensive studies have been carried out to investigate complications of brucellosis in different age groups (childhood, adult and middle aged). Previous descriptions of the complication patterns in patients with brucellosis have been based mainly either on series of adults or children cases. In this report, we describe the clinical presentations, laboratory findings and especially the range of complications in both children and adult cases with brucellosis in Southeastern Anatolia in Turkey.

MATERIALS AND METHODS

We carried out a retrospective analysis of patient records for 283 patients diagnosed with brucellosis between January 1992 and December 2000 in our hospital, which serves almost 5.5 million inhabitants in the region.

The diagnosis of brucellosis was established by satisfying one of the following criteria: (1) isolation of brucella species in blood or other body fluids or tissue samples (Bactec 9240, Becton-Dickson Diagnostic Instrument System, Sparks, USA); (2) a compatible clinical picture supported by the detection of specific antibodies at significant titres and /or demonstration of an at least fourfold rise in antibody titre in serum specimens taken over 2 or 3 weeks. A dilution titre of 1:160 or more was taken as positive for brucellosis (Brucella abortus M101, Barcelona, Spain).[17] Sera in all cases were diluted beyond 1:1280 to avoid prozone phenomenon.

All patients with brucellosis were investigated in more detail in respect to complications including skeletal, cardiovascular, pulmonary, abdominal, genitourinary, central nervous system, haematological, cutaneous and ocular. Focal complication was defined as the presence of symptoms or physical signs of infection at a particular anatomic site that lasted for at least 7 days in a patient with active brucellosis.

Radiographic examinations of the spine, of both sacroiliac joints in the prone position and in osteoarticular location with suspicious signs were performed for each patient. Osteoarticular involvement was diagnosed in instances of tenderness, restriction of movement and swelling in any peripheral joint, or by 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. However, swelling was not essential for the diagnosis of hip, spine or sacroiliac arthritis. Diagnoses of spondylitis and sacroiliitis were confirmed by computerized tomography (CT) or magnetic resonance imaging (MRI). Neurological complication was defined as any neurological symptom or sign not attributable to other causes with simultaneous isolation of Brucella spp. in the central nervous system, or as demonstration of intrathecal synthesis of specific antibodies. Neurological alterations caused by neighboring processes or asymptomatic alterations of cerebrospinal fluid (CSF) not accompanied by other inclusion criteria were excluded. Hematological complications were considered only as those with a defined clinical expression, excluding asymptomatic or poorly symptomatic cytopenias or coagulation disturbances. Hepatic complication was defined as the presence of a 5-fold or greater rise in normal levels of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) or greater with the presence of pain in the right upper quadrant or jaundice.

In addition, completed history and physical examinations of all patients were reviewed. A complete blood count, erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), C-reactive protein (CRP), blood chemistry profile and urine analysis were performed for all patients. In suspected cases the following tests were performed: echocardiography (ECHO) for heart involvement;

lumbar puncture, CT and / or MRI for meningitis; routine chest x-ray and thorax CT for pleural effusion and pneumonia; scrotal doppler ultrasonography (USG) for epididymoorchitis; abdominal USG and aspiration biopsy for ascites; bone marrow biopsy for differential diagnosis of pancytopenia; rectal USG and prostate biopsy for prostatitis; and pelvic and scrotal ultrasonography.

Based on the systemic disease duration before admission to hospital, patients were classified as acute (less than 2 months), subacute (2 - 12 months) and chronic (12 months).[18] Patients were classified into the following three groups according to their age: less than 15 years old (group A), 15-45 years old (group B) and over 45 years old (group C).

Two approaches were used for treatment in adult patients without complications:

1. Tetracycline (500 mg/6 h p.o.) or doxycycline (100 mg/ 12 h p.o.) for 45 days plus streptomycin (1 g/day i.m.) for the first 21 days.
2. Doxycycline (100 mg/12 h p.o.) plus rifampicin (15 mg/kg p.o.) for 45 days.

Children were treated with oral trimethoprim sulphamethoxazole (TM-SMX) or tetracycline for at least six weeks, in combination with intramuscularly streptomycin for the first three weeks or oral rifampicin for a minimum of six weeks. Tetracycline was only given to children older than eight.

Patients were followed up fortnightly until the end of the treatment period, monthly for three months, and thereafter every three months. Relapse after treatment was judged as either a recurrence of symptoms and signs of the disease, a positive blood culture or a rising antibody titer, in the absence of re-exposure to infection.

Statistical analysis

The data obtained were analyzed using the Statistical Package for the Social Sciences (SPSS). Chi-square test or Fisher's exact test, when the cell number was small, were used for categorical variables. A level of significance of <0.05 was considered significant.

RESULTS

Demographic information

Of the 283 patients, 138 (49%) were female and 145 (51%) male. Mean age was 32.69 ± 14.39 (range 2 - 72) years. The patient characteristics are presented in Table 1.

Source of Infection and Seasonal Distribution: The presumable infection source could be identified in 85% of patients in group A, 87% of patients in group B, and 89% of patients in group C. In this study, in 188 (66%) of the patient was dealing with stockbreeding. In all groups, the possible sources of infection were consumed, un-pasteurized dairy products, especially raw milk and fresh cheese, and direct contact with animals or working with animal products obtained from either sheep or goats. In group A the ingestion of raw milk / fresh cheese and of raw meatballs were less than in other groups ($p<0.05$). No source was identified in 38 (13%) patients (Table 1), most of whom were thought to have received the microorganism from raw meat or un-pasteurized milk. When the distribution of all cases was examined according to months of the year, an increase was seen in June (Fig. 1). There were no significant differences in the distribution of months among any of the groups.

Clinical features

Signs and symptoms of brucellosis in this series reflected a combination of systemic illness with certain manifestations. Table 1 lists the main symptoms and signs noted on presentation. Arthralgia, chilling, sweating, fever and malaise were the main presenting symptoms overall. There were significant differences among groups in respect to chilling, lumbar pain, lack of appetite and cough ($p<0.05$), whereas the other clinical parameters did not present any significant differences among the patient groups.

Physical examination findings

Hepatomegaly (28%) and splenomegaly (27%) were the most common, physical examination findings. Splenomegaly in group A was signifi-

Table 1. Epidemiologic and Clinical Characteristics in 283 Patients with Brucellosis by Age Group

Variable	Group A (n/%) 53 (19)	Group B (n/%) 178 (63)	Group C (n/%) 52 (18)	Total (n/%) 283 (100)
Sex				
Female	24 (8)	89 (31.5)	25 (9)	138 (49)
Male	29 (10)	89 (31.5)	27 (9)	145 (51)
Clinical type				
Acute	15 (28)	40 (22)	18 (35)	73 (25)
Subacute	30 (57)	107 (60)	27 (52)	164 (59)
Chronic	8 (15)	31 (17)	7 (13)	46 (16)
History				
Ingesting raw milk/ Fresh cheese*	28 (53)	143 (80)	34 (65)	205 (72)
Ingesting raw meat balls*	12 (23)	112 (63)	32 (62)	156 (55)
Animal contact	17 (32)	96 (54)	21 (40)	134 (47)
Family history brucellosis	18 (34)	83 (47)	20 (38)	121 (43)
Laboratory workers	-	2 (1)	-	2 (1)
Unknown transmission	8 (15)	24 (13)	6 (11)	38 (13)
Symptoms				
Arthralgia	44 (83)	149 (84)	39 (75)	231 (82)
Chilling*	34 (64)	158 (89)	36 (69)	228 (81)
Sweating	38 (72)	151 (85)	35 (67)	224 (79)
Fever	48 (90)	153 (86)	39 (75)	214 (76)
Malaise	52 (98)	102 (57)	50 (96)	204 (72)
Headache	50 (94)	102 (57)	36 (69)	188 (66)
Lumbar pain*	18 (34)	118 (66)	36 (69)	172 (61)
Myalgia	47 (89)	81 (46)	43 (83)	171 (60)
Lack of appetite*	44 (83)	56 (31)	40 (77)	140 (49)
Cough*	40 (75)	20 (11)	27 (52)	88 (31)
Vomiting	13 (25)	25 (14)	13 (25)	52 (18)
Rash	14 (26)	21 (12)	14 (27)	49 (17)
Jaundice	7 (13)	23 (13)	5 (10)	35 (12)
Abdominal pain	19 (36)	30 (17)	6 (12)	55 (19)
Constipation	4 (7)	15 (8)	6 (12)	25 (9)
Diarrhea	3 (6)	6 (3)	2 (4)	11 (4)
Depression	-	4 (2)	6 (12)	10 (4)
Scrotal pain	1 (2)	10 (6)	3 (6)	14 (5)
Signs				
Hepatomegaly	22 (42)	41 (23)	15 (29)	78 (28)
Splenomegaly*	29 (55)	38 (21)	9 (17)	76 (27)
Lymphadenopathy	5 (9)	12 (7)	5 (10)	22 (8)
Nuchal rigidity	1 (2)	8 (4)	1 (2)	10 (4)

*Indicates significant differences among groups ($p<0.05$).

cantly higher than in groups B and C ($p<0.05$). Nuchal rigidity presented in ten patients, 8 of whom had meningitis (Table 1).

Laboratory findings

Most patients with normal leukocyte and lymphocyte counts were not thrombocytopenic, and had normal or mostly elevated ESR. The patients with leukopenia in group A had higher ESR than other groups. In all groups, white blood cells (WBC) of 77% of patients were between 4,000 and 10,000. In group A the ratio of patients with anemia was less than that of other groups ($p<0.05$), while the rate of patients with elevated ALT and AST in group B was less than that of groups A and C ($p<0.05$). In addition, the rate of elevated ESR in group B was less than in other groups ($p<0.05$) (Table 2).

Complications

Osteoarticular complications were the most frequent focal forms, being present in 195 cases, representing 69% of all patients. Of the 283, two hundred thirty-one patients had arthralgia in joints other than the joints affected by arthritis. The arthralgia manifested as intermittent or migratory pain of large or small joints, or both, with or without limitation of movements. The axial skeleton was the most common site (86%). The most commonly affected joint was the sacroiliac joint (108 patients, 55%), with predominantly unilateral involvement ($p<0.05$). Total sacroiliitis was more frequent in group B (39%) than in groups A (9%) and C (7%) ($p<0.05$), but there was no significant difference between groups A and C in respect to sacroiliac involvement. The second most affected joint type in patients with musculoskeletal involvement was peripheral joints (54%), with the hip (58%) and knee (22%) being the most commonly affected. The maximum rate of peripheral joint involvement was in group B ($p<0.05$). In group A hip involvement was less frequent than in groups B or C ($p<0.05$), while in group A knee involvement was significantly greater group B as well as group C ($p<0.05$). Other less commonly affected joints were the ankle (7%), shoulder (6%), elbow (4%), sternoclavicular (2%), wrist (1%) and small joints (1%). Sixty patients (31%) had spondylitis, at a higher rate in group B (15%) than the others.

Cutaneous complications (17%) were most common, followed by genitourinary (8%), nervous (7%) and respiratory (5%). Hematological, gastrointestinal, cardiovascular and sepsis were rare complications and no case of ocular complication was shown (Table 3).

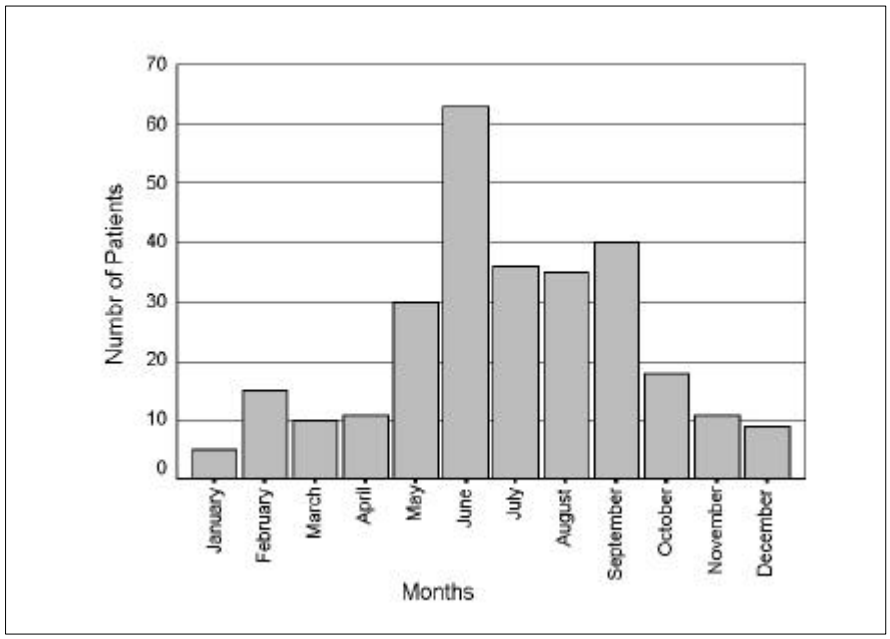

Fig. 1. Distribution of 283 cases with brucellosis by months of the year.

Table 2. Hematological Findings in 283 Patients with Brucellosis by Age Group

Laboratory	Group A (n/%)	Group B (n/%)	Group C (n/%)	Total (n/%)
White blood cells/mm^3				
<4000	14 (27)	16 (9)	10 (19)	40 (14)
4000 - <10000	34 (64)	146 (82)	39 (74)	219 (77)
≥10000	5 (9)	16 (9)	3 (6)	24 (8)
Lymphocytes ≥40%	22 (42)	41 (23)	26 (49)	90 (32)
Anemia (male>13, female >12 g/dl)*	32 (60)	126 (69)	41 (79)	199 (70)
ALT (>40 IU/L)*	33 (62)	41 (23)	35 (66)	109 (39)
AST (>40 IU/L)*	35 (66)	47 (26)	42 (79)	124 (44)
CK (>174 IU/L)	19 (36)	19 (11)	14 (26)	52 (18)
CRP (>6 mg/l)	34 (64)	138 (78)	37 (70)	209 (74)
ESR (40 mm/h)	33 (62)	49 (28)	33 (62)	115 (41)
Rheumatoid factor	10 (19)	31 (17)	24 (45)	65 (23)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
*indicates significant differences among groups ($p<0.05$).

Clinical outcome

Treatment failed in 15 patients (5%), owing to true relapse in ten and to non-compliance and drug side effects in the other five. These 15 patients recovered after a new regimen was used. No mortality was registered in our patients. Two hundred seventy-two patients received medical treatment alone and 11 required medical and surgical treatment as well (9 spondylitis and 2 carditis). Two drugs were used for 3 - 6 months in patients with complications and three-drugs were used for the same period in patients associated with meningitis and carditis.

DISCUSSION

The incidence of brucellosis has increased during recent years due to the inability to complete its eradication among the animals of Turkey, especially sheep and goats.[19] Determining the incidence and prevalence of brucellosis in animals and humans is very difficult because formal records of brucellosis are insufficient in our country. Our hospital is located in South-eastern Anatolia of Turkey, where most people usually consume un-pasteurized dairy products collected from villages. Raw meatball is a local delicacy in Southeastern Anatolia and its ingestion might transfer the disease. *B. melitensis* occurs primarily in goats and sheep, the most commonly raised animals in Southeastern Anatolia.[4] *B. melitensis* was the most common etiologic agent in our study.

Since most patients had used antibiotics effective on brucella infection before they were admitted to our hospital, the rate of isolation of microorganism from blood culture was found to be low. Only 25% of our patients had positive culture for brucella species, mostly being *B. melitensis*.

When the distribution of the cases according to months of the year was examined, an increase was seen in the spring and summer months, possibly due to the increased consumption of milk and fresh cheese in spring. However, as far as we know no studies have investigated the seasonal distribution of brucellosis.

Brucellosis can occur at any age but is most common in adolescents and young adults.[10,20,21] In this study, 63% of the patients were between 15

Table 3. Complications in 283 Patients with Brucellosis by Age Group

Complications	Group A (n/%)	Group B (n/%)	Group C (n/%)	Total (n/%)
Skeletal system	39 (14)	122 (43)	34 (12)	195 (69)
Sacroiliitis	19	76	13	108
Peripheral arthritis	19	69	18	106
Spondylitis	7	30	23	60
Periarticular inflammation	2	5	2	9
Osteomyelitis	-	1	1	2
Cutaneous system				
Rash	14 (21)	21 (14)	14 (20)	49 (17)
Genitourinary system	1	14	6	21 (8)
Orchiepididymitis*	1	10	3	14
Pyelonephritis	-	2	2	4
Prostatitis*	-	2	1	3
Nervous system	2	10	7	19 (7)
Meningitis	1	6	1	8
Encephalitis	1	-	-	1
Depression	-	4	6	10
Respiratory system	5	7	3	13 (5)
Bronchitis	2	2	1	5
Pneumonia	2	2	-	4
Pleural effusion	1	2	1	4
Hematologic system	4	5	3	12 (4)
Thrombocytopenia	2	3	2	7
Pancytopenia	1	2	1	4
Hemolytic anemia	1	-	-	1
Gastrointestinal system	-	4	3	7 (2)
Hepatitis	-	2	1	3
Ileitis	-	1	1	2
Ascites	-	1	1	2
Cardiovascular system				
Carditis	-	2	-	2 (1)
Sepsis	1	2	-	3 (1)
More than one complications	15 (28)	35 (20)	20 (38)	70 (25)

*In a sample of 145 males.
(The rates in the table are displayed separately for each complication for each patient who was individually evaluated).

and 45 years and 19% were between 7 and 14 years. These results clearly show how the age range reflects the magnitude of the socio-economic and cultural impact of brucellosis in our region of Turkey.

Each sex is equally affected,[4,10,19] though brucellosis has long been recognized to be an occupation-related disease primarily affecting adult

men.[22] Some investigators have reported more severe forms of the disease in women,[23] but this finding has not been confirmed yet.[14,19]

Brucellosis usually presents non-specific clinical manifestations such as fever, malaise, sweating, hepatomegaly or splenomegaly.[10,16,20,24] In total patients, arthralgia and chilling were the most frequent symptoms, whereas malaise and headache in children, chilling and fever in adults, and malaise, fever and arthralgia in older aged. Hepatomegaly and splenomegaly were the most common signs in all groups and splenomegaly was more frequent in group A than the rest.

Routine laboratory data reported in most studies have been of little diagnostic value.[19,25] Hematological and biochemical testing yielded no specific findings to suggest the diagnosis of uncomplicated or focal brucellosis. In our study, WBC counts of most cases (77%) was between 4000 and 10,000/mm^3 and leukocytosis was rare (8%). Over one third of patients had high ALT and AST levels in all age groups, especially over 45 years. The following values of AST and ALT are important due to the hepatotoxic effect of rifampicin and tetracycline. In our study, CRP and anemia were lower while creatine kinase (CK) was higher in the child group than the other groups. The number of patients with RF positive was positively correlated with age.

Brucellosis can affect virtually any organ or system causing focal forms with long clinical courses, which are considered true complications of the infection. Notable discrepancies exist in the incidence rate and clinical spectrum of focal forms. Reported incidence rates range from less than 1% in some series to more than 50% in others.[26] Therefore, these discrepancies seem to be mainly related to the retrospective character of the reports and the lack of uniform definitions and diagnoses of focal forms.[20]

Among complications, osteoarticular involvement is seen as the most frequent complication of brucellosis.[10,14,16,24,27-29] However, its prevalence has varied from 0%[26] to 69%.[29] The diversity of criteria used for the diagnosis of skeletal involvement in brucellosis may have caused the variations in the results obtained by different researchers. In our study the 69% ratio of patients with skeletal complications of brucellosis (195 cases) was equal to the highest previously reported incidence. Brucellosis may also affect the musculoskeletal system at any site.[4,10,20] We found that the most commonly affected site was the sacroiliac joint (55%), a finding in agreement with those recently reported by some authors.[10,12,19,30] Peripheral arthritis, especially presenting as monoarthritis, is the predominant involvement in some brucellosis series and occurs more frequently in children and young adults. Large joints, such as the hips, knees and ankles are the most frequently affected.[10,31] In our series, peripheral arthritis was the second most frequent type of osteoarticular involvement, although the rate (54%) was higher than in other studies which ranged from 14 - 19.5%.[3,9,16,26] On the other hand, the incidence of spondylitis reported in the literature varies significantly, ranging from 6% to greater than 50%.[16,19,22] It is seen especially in elderly men over 50 years of age. In the present study, the rate of spondylitis was 31%, with the rates in childhood (4%) and the elderly (12%) being slightly lower than in adults (18%) in the 195 patients. However, of 34 elderly patients, 23 (68%) had spondylitis.

In the present study, cutaneous complication was the second most frequent after osteoarticular complication. Cutaneous lesions of brucellosis are rare and occur in about 5% of patients with brucellosis.[32] In our study, the frequency of cutaneous lesions (17%) was higher than previous studies.[3,32] In 93% of cases with cutaneous lesions, the lesions were maculopapular or papulonodular exanthema, involving predominantly the lower limbs and trunk, while only two patients (4%) had a true skin complication.

Genitourinary involvement occurs in 2 - 40% of patients with brucellosis.[20,33] Recently, epididymitis or orchitis have been reported in different studies.[4,33] Epididymitis and orchiepididymitis start subacutely, and in contrast to nonspecific orchiepididymitis, frequently have associated systemic symptoms, minimal urinary symptoms, lower WBC counts and fewer alterations in the urine sediment.[33] Orchids occur in up to 20% of men with brucellosis,[34,35] but are an important focal form of human brucellosis, which may cause serious complications. The genitourinary complications of brucellosis usually respond favorably to treatment, but testicular atrophy and abscesses

requiring surgical treatment have been described. In addition, interstitial nephritis, pyelonephritis and exudative glomerulonephritis have been reported.[36,37] In our study, 21 of (8%) 283 patients had genitourinary complications. Many cases (67%) with genitourinary complications were orchiepididymitis and all these patients were treated medically. Pyelonephritis and prostatitis were other complications. In our experience, genitourinary involvement, especially orchiepididymitis may be curable by medical therapy if diagnosed early, and these patients therefore do not need surgical interference.

Nervous system complications include meningitis, encephalitis, myelitis-radiculoneuritis, brain abscess, epidural abscess, demyelination syndromes and meningovascular syndromes.[4] The reported incidence of neurological complications ranges from 0% to 25%.[26,38] It is difficult to know how frequently the nervous system is affected, because of difficulties in diagnosis and variability in reporting such complications.[39] These marked discrepancies derive mainly from the inclusion in some of the series of spinal cord and radicular compressions produced by contiguous osteoarticular processes. In the present study, the incidence was 3%, after the 10 cases with depression were excluded; a finding similar to that reported in other studies using similar diagnostic findings.[20,40-42] Meningitis is the most frequent central nervous system complication, and it can be the presenting finding or it can occur late in the course of the disease. A high cure rate can be achieved by treatment with triple combination in these diseases (tubercular meningitis, viral encephalitis, aseptic meningitis), which otherwise have a high mortality and morbidity. Our cases used doxycycline (100 mg/12 h p.o.) plus rifampicin (15 mg/kg p.o.), in combination with either ceftriaxone or TM-SMX, for 3 - 6 months until CSF had been cleared. A high degree of suspicion is prudent for the diagnosis. All of our patients recovered without complication. The prognosis of meningitis is usually good; however, in cases of encephalic or spinal cord involvement, mortality is not negligible and sequela is frequent[42,43] Psychiatric disturbance, most commonly depression, is frequent in brucellosis. Although depression and mental inattention are common complaints in brucellosis, direct invasion of the central nervous system occurs in less than 5% of cases.[44] In our cases the frequency of depression was low. Most of the patients with depression were chronic patients. Such patients with complication may be evaluated in detail because of problems with treatment compliance.

Respiratory involvement in brucellosis may occur following inhalation of infectious aerosols, and possibly via bacteremic spread of the organism to the lungs. The presence of a dry or scarcely productive cough is a frequent symptom in patients with brucellosis but does not imply the existence of a focal complication.[20] About 15 - 25 percent of patients with brucellosis develop a cough or other respiratory symptoms.[46] Hilar and paratracheal lymphadenopathy, pneumonia, solitary or multiple pulmonary nodules, lung abscesses and empyema have been reported.[20,45] There were patients with bronchitis, pneumonia and pleural effusion in our study groups, who were cured by standard antibiotic therapy. The pleural effusion patients had this treatment regimen for 3 months.

Hematologic alterations in brucellosis are common,[23,46] but they rarely constitute a true complication and resolve promptly with treatment. The hematological manifestations of brucellosis include anemia, leucopenia, thrombocytopenia and clotting disorders.[47] Leucopenia was detected in 16%, and relative lymphocytosis in 32%, of our patients. Pancytopenia occurs in 5 - 20% of patient with brucellosis.[23,48] There are isolated reports of severe autoimmune hemolytic anemia.[20] In our study, seven patients had thrombocytopenia, four pancytopenia and one hemolytic anemia (child patient).

Hepatic and splenic enlargement may be documented in 15 to 20% of cases, and abscesses may develop in the liver and spleen. Liver involvement is very frequent in brucellosis, although this involvement usually has little clinical importance and is usually limited to soft painless hepatomegaly or slight increases in levels of aminotransferases.[49,50] These clinical and biochemical abnormalities are completely reversed with adequate treatment. Liver abscess is uncommon in brucellosis. In addition to hepatic involvement, digestive system complications of brucellosis are

exceptional, although cholecystitis, ileitis, colitis and pancreatitis have been reported.[20] In the present study, there were no hepatic or splenic abscesses but 1 case of ileitis and 2 of ascites were detected. Ascites has not been reported as a complication of brucellosis in other studies. The ascitic fluids of the patients were found to be exudative.

Cardiovascular complications are rare, occurring in less than 2% of patients with brucellosis in large series[9,26] and 1% in our series (1 aortic valve and 1 mitral valve). They include endocarditis, myocarditis, and pericarditis.[20,51,52] The mortality rate for brucellosis is less than 1% with cardiovascular complication, which accounts for 80% of these deaths. Although a complete cure has occasionally been achieved with medical treatment alone, most require surgical treatment because of homodynamic instability. We treated these cases both medically and surgically because early surgical intervention during the active phase of infection is safe. Medical therapy for brucella carditis consists of a combination of antibiotics used for a long period. Although the optimal combination and duration are unknown, we used doxycycline, rifampicin and TM-SMX for 6 months. None of our patients died. In addition, we detected three sepsis cases in brucellosis although it has not been in previously reported.

Because 25% of all patients with brucellosis had more than one complication, complications of brucellosis were most frequent in our cases. This situation was more predominant in group C (38%) than in group A (28%) or B (20%). Cutaneous, hematological and respiratory complications in childhood; osteoarticular and cardiac complications in adults; and genitourinary, neurological and gastrointestinal complications in middle aged were more prominent.

In brucellosis, the aim of a treatment regimen is to control the acute illness and to prevent both complications and relapse. Treatment of patients should be prolonged since the eradication of organism from bone or other organs may be difficult. Treatment with only a single agent and of short duration carries a high risk for relapse. We did not treat with a single agent, nor did we use quinolone antibiotics, so our relapse rate was low (3.5%). In addition, there were no significant differences among the treatment regimes.

In conclusion, the frequency of brucella complications was variable in different age groups in Southeastern Anatolia of Turkey. The most frequent complication of brucellosis was osteoarticular, followed by cutaneous, genitourinary, nervous and other complications. Since brucellosis is a preventable disease, knowledge and early diagnosis of the complications are especially important. Therefore, population education and medical precautions are necessary to prevent the harmful effects of brucella and its complications. In addition, primary health care physicians should be alerted regarding the clinical and laboratory findings of brucella complications.

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