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Musculoskeletal involvement in brucellosis in different age groups: a study of 195 cases

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Summary

Objective: The aim of the present study was to determine the distribution and characteristics of arthritis in 195 patients with musculoskeletal involvement due to brucellosis in different age groups in the southeastern region of Turkey.

Patients and methods: We carried out a retrospective analysis of 283 patients with brucellosis records and identified 195 with musculoskeletal involvement. Patients were classified into acute-subacute (<12 months) and chronic (>12 months) brucellosis. Patients were also classified into three age groups: <15 years old (group A), 15–45 years (group B), and over 45 years (group C). In addition, patients were classified into five subgroups according to type of arthritis: peripheral arthritis, polyarthritis, spondylitis, sacroiliitis, and spondylitis/sacroiliitis.

Results: 195 (69%) of the 283 patients [138 female (49%), 145 male (51%)] had musculoskeletal involvement. Of the patients with musculoskeletal involvement 113 (58%) were female and 82 (42%) were male, ranging in age from 3 to 71 years (mean age 33.14 ± 15.03). Of 195 patients studied, 39 (14%) were <15 years old (group A), 122 (43%) were aged 15–45 (group B), and 34 (12%) were over 45 (group C). The most commonly affected joints were the sacroiliac joint in 108 patients (55%), peripheral joints in 106 (54%), and spondylitis in 60 (31%). Of 108 patients with sacroiliitis, 19 were in group A, 76 in group B, and 13 in group C. Bilateral sacroiliitis was less common in group B (23 patients) than in groups A (3) and C (3) ($p < 0.05$). Spondylitis was more common in group B (18%). Sacroiliitis and polyarthritis were more common than other types of musculoskeletal involvement in females, whereas in males the distribution of all types was similar. In patients aged under 15 and 15–45, sacroiliitis and polyarthritis were common compared with other types of arthritis, but the distribution was similar in patients over 45.

Conclusion: In southeastern Anatolia musculoskeletal involvement in brucellosis is frequent. The series presented suggests that musculoskeletal involvement in group A is higher than groups A and C. The prevalence of musculoskeletal involvement appears to differ according to age, sex and clinical type.

Key words: arthritis; brucellosis; musculoskeletal involvement; age

Introduction

Brucellosis occurs naturally in domestic animals. It is still an important public health problem throughout the world, but principally, and in particular, in the Mediterranean region, including Turkey, the Arabian peninsula, the Indian subcontinent, Mexico, and parts of Central and South America [1–3]. Human infection is contracted from infected animals and closely linked to poor animal husbandry methods, feeding habits, and hygiene standards [4]. The disease typically attacks young and middle-aged adults, with a low incidence among infants and elderly patients [5–7].

The clinical manifestations of brucellosis are protean and include rheumatic complaints in 20–85% of patients. Musculoskeletal complications are important owing to their high prevalence and also the associated functional sequelae [8, 9]. The prevalence and pattern of musculoskeletal involvement depend on the strain of *Brucella* infecting the individual, the patient's age and the duration of the disease [10–19]. Comparative and statistical studies in large populations and in different age groups are therefore highly important. Although there are many reports on brucellosis in

adulthood or childhood [9, 13, 18, 19], as far as we know no comprehensive studies have been carried out to investigate musculoskeletal involvement in brucellosis in different age groups (childhood, adulthood, middle/old age) in the English-speaking literature. Previous descriptions of the musculoskeletal pattern in patients with brucellosis have been chiefly based either on series of adults or children. In this report we describe the clinical presentation and characteristics of musculoskeletal involvement in both children and adults with brucellosis.

The aim of the present study was to evaluate the distribution and characteristics of arthritis in 195 patients with musculoskeletal involvement due to brucellosis in different age groups in the southeastern region of Turkey.

Patients and methods

We carried out a retrospective analysis of 283 patients with brucellosis records in the period January 1992–December 2000 and identified 195 patients with musculoskeletal involvement in our hospital, which serves a population of almost 5.5 million in the southeastern region of Turkey.

Brucellosis was diagnosed on the basis of one of the following criteria: (1) isolation of *Brucella* species in blood, other body fluids or tissue samples (BACTEC 9240, Becton-Dickson Diagnostic Instrument System, Sparks, USA); (2) a compatible clinical picture such as athralgia, fever, sweating, chills, headache, and malaise 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. Significant titres were determined to be ≥1/160 in the standard tube agglutination test (SAT) (*Brucella abortus* M101, Cromatset, Linear Chemicals, Spain) [20].

A radiographic study of the spine, of both sacroiliac joints in the prone position and another musculoskeletal location with suspicious signs was performed for each patient. Radiological findings of sacroiliitis were recorded as a poorly defined subchondral osseous line, narrowing or widening of the interosseous line and narrowing or widening of the interosseous space. For spondylitis, the radiographic findings were recorded by determining epiphysitis of the anterosuperior angle of the vertebra, narrowing of the disc space, erosion, sclerosis, vertebral collapse and osteomyelitis. A radionuclide bone scan with technetium-99 methylene diphosphate was performed when clinical suspicion was strong and the radiographic examination was normal. Criteria for evaluation of the bone scans were qualitative rather than quantitative. Increased uptake in an affected site was considered to be positive.

Musculoskeletal involvement in the form 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, was evaluated independently by both the clinician and the radiologist. Swelling was not essential for the diagnosis of hip, spine, or sacroiliac arthritis, however. Additional signs such as effusion, warmth, and redness, though encountered in many cases, were not considered essential for the diagnosis of arthritis. Clinically, sacroiliitis is recorded through either the Fabere test or by direct pelvic compression. Diagnoses of spondylitis and sacroiliitis were confirmed by computed tomography (CT) or magnetic resonance imaging (MRI).

In addition, the complete 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 in all patients.

Based on the systemic disease duration before admission to hospital, cases were classified as acute-subacute brucellosis (<12 months) and chronic brucellosis (>12 months). Attempts to categorise the disease into acute-subacute and chronic, according to the length and severity of symptoms, are purely arbitrary. Chronic brucellosis is usually caused by persistent deep foci of infection, such as suppurative lesions in the bone, joints, liver, spleen, or kidneys. Patients were classified into three age groups: <15 years (group A), 15–45 (group B) and over 45 (group C). In addition, patients were classified into five subgroups according to type of arthritis: peripheral arthritis, polyarthritis (more than two different sites), spondylitis, sacroiliitis, and spondylitis/sacroilitis

Several approaches were used for treatment in adult patients:

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.

Doxycycline (100 mg/12 h p.o.) plus rifampicin (15 mg/kg p.o.) for 45 days.

Children were treated with oral trimethoprim, sulphamethoxazole or tetracycline for at least six weeks in combination with intramuscular streptomycin for the first three weeks or oral rifampicin for a minimum of six weeks. Tetracycline was given only to children aged over 8.

In patients with spondylitis, one of these schedules was given for at least 3 months. Patients were followed up fortnightly until the end of the treatment period, monthly for three months, and thereafter every three months for one year. Relapse was assessed by a recurrence of symptoms and signs of the disease, a positive blood culture or rising antibody titre after treatment, in the absence of re-exposure to infection.

Statistical analysis

The data obtained were analysed using the Statistical Package for the Social Sciences (SPSS). One-way ANOVA and post-hoc tests were used for multiple comparison. In addition, the χ^2-test and Fisher's exact tests (when appropriate) were used for categorical variables, and Student's t-test was used to compare mean values. Differences in the p value of <0.05 were considered significant.

Results

In our study, 283 (145 male and 138 female) patients with brucellosis were analyzed and 195 patients with musculoskelatal involvement were included. Of 195 patients, 113 were female (58%) and 82 were male (42%), ranging in age of 3 to 71 years (mean age 33.14 ± 15.03). These patients were evaluated in three different groups. Thirty nine patients (14%) who were younger than 15 years old were grouped as group A, 39 patients were between 15 to 45 years old 122 patients (43%) were group B and older than 45 years old 34 patients (12%) were group C. Although the rate of female patients were significantly higher than male in group B ($p < 0.05$), there was no significant differences between other groups (table 1).

Table 1

Sites and rates of involvement in the 195 patients with musculoskeletal involvement.[a]

Variable	group A n (%)	group B n (%)	group C n (%)	total n (%)
Sex				
Female	19 (49)	76 (62)[c]	18 (53)	113 (58)
Male	20 (51)	46 (38)	16 (47)	82 (42)
Clinical type				
Acute	34 (87)[c]	72 (59)	21 (62)[c]	127 (65)[c]
Chronic	5 (13)	50 (41)	13 (38)	68 (35)
Musculoskeletal involvement[b]	39 (20)	122 (63)	34 (17)	195 (100)
Sacroiliitis[b]	19 (9)	76 (39)	13 (7)	108 (55)
Unilateral	16 (84)[c]	53 (70)[c]	10 (77)[c]	79 (73)[c]
Bilateral	3 (16)	23 (30)	3 (23)	29 (27)
Peripheral arthritis[b]	19 (9)	69 (36)	18 (8)	106 (54)
Hip[b]	8 (42)[c]	42 (61)[c]	11 (61)[c]	61 (58)[c]
Knee[b]	7 (37)	14 (21)	2 (10)	23 (21)
Ankle	2 (11)	5 (7)	1 (6)	8 (7)
Shoulder	–	4 (6)	2 (11)	6 (6)
Elbow	1 (5)	2 (3)	1 (6)	4 (4)
Sterno-clavicular	1 (5)	1 (1)	–	2 (2)
Small joints	–	–	1 (6)	1 (1)
Wrist	–	1(1)	–	1 (1)
Spondylitis	7 (4)	30 (15)	23 (12)	60 (31)
Lumbar	6 (86)[c]	25 (83)[c]	18 (78)[c]	49 (82)[c]
Dorsal	1 (14)	4 (13)	3 (13)	8 (13)
Cervical	–	1 (4)	2 (9)	3 (5)
Periarticular inflammation	2 (1)	5(3)	2 (1)	9 (5)
Osteomyelitis	–	1(0.5)	1(0.5)	2 (1)

[a] 195 patients have musculoskeletal involvement in 285 sites
[b] ANOVA test shows significant differences among groups ($p < 0.05$)
[c] ANOVA test shows significant differences within subgroups ($p < 0.05$)

Arthritis occurred for the first time on all patients within one week before admission to hospital. This was one of the main presenting clinical features. Joint effusion occurred in 37 of 195 (19%) patients predominantly in acute (86%). The effusion was elicited in knee, ankle, shoulder, elbow, and wrist in descending order. Joint effusion in patients clinically suspected was detected by ultrasonography or MRI

The most commonly affected joints were the sacroiliac (108 patients, 55%), with predominantly unilateral involvement ($p < 0.05$). Sacroiliitis was bilateral only in 29 patients (27%). Total sacroiliitis was more frequent in group B (39%) than in groups A (9%) and C (7%) ($p < 0.05$). There was no significant difference between groups A and C ($p < 0.05$). Bilateral sacroiliitis was more frequent in group B (23 patients) than in groups A (3) and C (3) ($p < 0.05$).

The second most affected joints in patients with musculoskeletal involvement were peripheral joints (54%). Of 106 patients with peripheral arthritis, 75 (69%) had monoarthritis. Hip (58%) and knee (22%) were the most commonly affected peripheral joints. 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 and C ($p < 0.05$), while in group A knee involvement was significantly greater than in other groups ($p < 0.05$). Other less commonly affected joints included ankle (7%), shoulder (6%), elbow (4%), sternoclavicular (2%), wrist (1%), and small joints (1%). 60 patients (31%) presented spondylitis, at a higher rate in group B *(15%)* than in the others. In *49* of 60 patients with spondylitis (80%), the spondylitis was lumbar. Plain radiographs obtained from 49 patients (82%) showed signs similar to spondylitis and 11 patients (18%) had a normal plain radiograph but a positive bone scan. CT and/or MRI scan were obtained for all patients with spondylitis. Periarticular inflammation including bursitis and tendinitis were present in nine patients. Two female patients with arthritis of the hip had osteomyelitis of the adjacent proximal end of the femur; in operative decompression debridement and drainage of the hip joint was necessary.

Sacroiliitis and polyarthritis were more common than other types of musculoskeletal involvement in females, whereas all types showed a similar distribution in males (figure 1). Sacroiliitis and

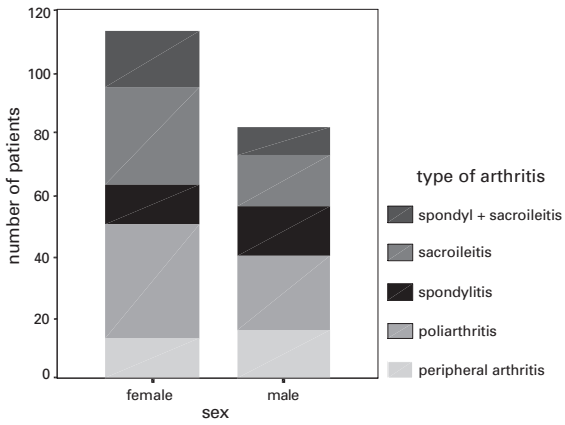

Figure 1

Types of arthritis in 195 patients with musculoskeletal involvement according to sex.

polyarthritis were more common than other types of arthritis in groups A and B, but in group C the distribution of arthritis types was similar (figure 2). Sacroiliitis and polyarthritis were more frequent in acute cases, and polyarthritis in chronic cases. Moreover, sacroiliitis + spondylitis was more common in chronic than in acute cases (figure 3).

Table 2 lists the main symptoms and signs noted on presentation. Arthralgia (84%), chills (82%), sweating (81%), fever (80%) and malaise (77%) were the main presenting symptoms. Splenomegaly (28%) and hepatomegaly (26%) were the most common signs. Arthralgia manifested as intermittent or migratory pain of large or small joints or both, with or without limitation of movement.

Table 3 shows the radiographic abnormalities in patients with musculoskeletal involvement. During the observation period, 117 patients (60%) had radiographic abnormalities. Of 108 patients with sacroiliitis, plain radiographs were abnormal in 81 (75%) and normal in the remaining 27 (25%). However, radionuclide bone scans in these 27 patients showed abnormalities. All patients had periarticular soft tissue swelling; however, four exhibited radiographic signs such as joint space narrowing and soft-tissue swelling.

The mean disease duration was 34.15 ± 21.36 days. Most of the patients had an acute presentation. In most patients' clinical response, subsidence of fever and arthralgia was seen after 5–10 days of treatment. Resolution of organomegaly and arthritis was slower (5–7 weeks). Generally speaking, in patients with spondylitis and sacroiliitis the arthritis took longer to resolve than in others. Treatment failed in ten patients (3.5%) owing to true relapse in six and non-compliance or drug side effects in the others. These patients recovered

Figure 2

Types of arthritis in 195 patients with musculoskeletal involvement according to age groups.

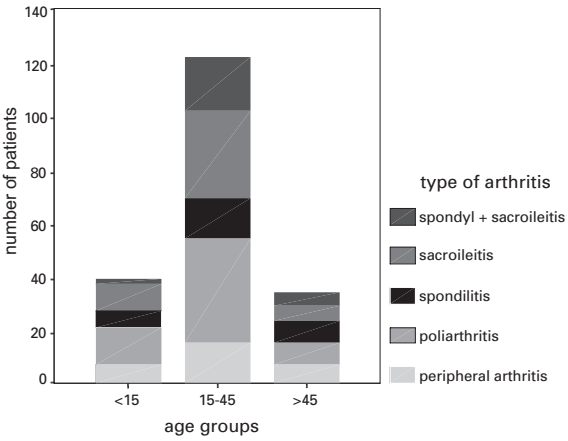

Figure 3

Types of arthritis in 195 patients with musculoskeletal involvement according to clinical types.

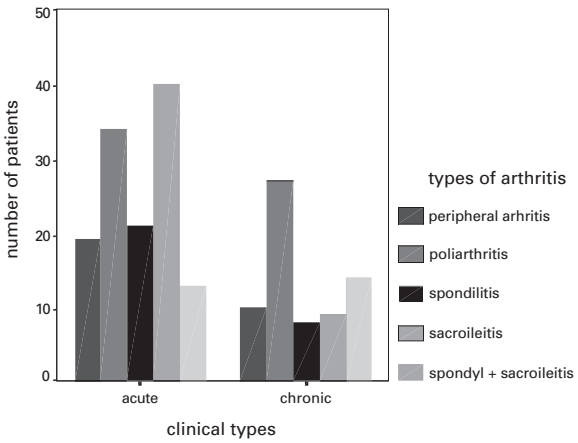

Table 2

Symptoms, signs and laboratory at initial examination in 195 patients with musculoskeletal involvement.

Variable	total n (%)
Clinical type	
Acute	127 (65)
Chronic	68 (35)
Symptoms	
Arthralgia	164 (84)
Chills	160 (82)
Sweating	158 (81)
Fever	158 (81)
Malaise	150 (77)
Headache	135 (69)
Lumbar pain	123(63)
Myalgia	121 (62)
Lack of appetite	101 (52)
Cough	50 (26)
Vomiting	35 (18)
Rash	30 (15)
Jaundice	21 (11)
Signs	
Splenomegaly	55 (28)
Hepatomegaly	51 (26)
Lymphadenopathy	15 (8)
Orchitis	10 (5)
Meningitis	6 (3)
Pleural effusion	3 (2)
Prostatitis	3 (2)
Carditis	2 (1)
Laboratory	
WBC (/mm^3)	
<4000	34 (17)
4000–10 000	144 (74)
≥10 000	17 (9)
Lymphocytes ≥%40	59 (30)
Anaemia(male >12, female >10 g/dl)	151 (77)
ALT (>40 IU/L)	80 (41)
AST (>40 IU/L)	78 (40)
CK (>174 IU/L)	39 (20)
CRP (>6 mg/l)	149 (76)
ESR (40 mm/h)	82 (42)
Rheumatoid factor	43 (22)

WBC: white blood cells, ALT: aspartate aminotransferase, AST: alanine aminotransferase, CK: creatine kinase, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate

Table 3

Radiographic abnormalities in the 195 patients with musculoskeletal involvement.

Variable	group A n (%)	group B n (%)	group C n (%)	total n (%)
Sacroiliitis	19 (10)	76 (39)	13 (7)	108 (55)
Poorly defined joint	10 (53)	50 (66)	7 (54)	67 (62)
Joint space narrowing	7 (37)	45 (59)	7 (54)	59 (55)
Joint space widening	4 (21)	16 (21)	5 (38)	25 (23)
Subchondral erosion	6 (32)	10 (13)	4 (31)	20 (19)
Sclerosis	3 (16)	6 (8)	3 (23)	12 (11)
Ankylosis	–	4 (5)	2 (15)	6 (6)
No anomalies	2 (11)	10 (13)	1 (8)	13 (12)
Peripheral arthritis	19 (9)	69 (36)	18 (8)	106 (54)
Joint space narrowing	8	20	7	35 (33)
Soft tissue swelling	6	14	4	24 (23)
No anomalies	6	38	10	54 (51)
Spondylitis	7 (4)	30 (15)	23 (12)	60 (31)
Disc involvement	2	19	10	31 (52)
Anterosuperior epiphysitis	2	15	12	29 (48)
Intervertebral space narrowing	2	15	11	28 (47)
Vertebral body destruction	1	13	11	25 (42)
Soft tissue abscess	1	7	6	14 (23)
Interapophysial involvement	1	6	2	9 (15)
No anomalies	1	1	2	4 (7)
Periarticular involvement	2 (1)	5(3)	2 (1)	9 (5)
Soft tissue swelling	1	2	1	4 (44)

after changing to a new regimen. No sequelae or mortality were registered in our patients. As mentioned under the Patients and Methods heading, patients were successfully cured with one of the treatment regimens. We found no significant differences among the various therapy regimens.

Discussion

The incidence of brucellosis has increased in recent years due to the impossibility of eradicating it completely in our country among animals and especially sheep and goats [2, 19, 21]. In our region the commonest aetiological agent for brucellosis is *B. melitensis*. Our hospital is located in southeastern Anatolia (Turkey), where the majority of the population usually consume unpasteurised dairy products collected from villages. Raw meatball is a local food speciality in southeastern Anatolia, ingestion of which may also transmit the disease.

Brucellosis can occur at any age but the most common age groups involved are adolescents and young adults [3, 10, 22]. In this study the disease mainly affected the most productive group in the community, because most of the patients with or without musculoskeletal involvement were aged between 15 and 45 years in the adult group and between 7 and 14 years in children. These results clearly show how the age range reflects the magnitude of the socio-economic and cultural impact of brucellosis in our region and Turkey.

The sexes are affected equally [10, 19, 23], though brucellosis has long been recognised as an occupational disease primarily affecting adult males [24]. In our study, females (58%) – especially in group B – are slightly but not significantly in the majority among patients with musculoskeletal involvement, although in the overall patient group both sexes are affected equally. Some investigators have reported more severe forms of the disease in women [25], but this finding has not yet been confirmed [17, 19].

Brucellosis with or without musculoskeletal involvement usually presents non-specific clinical manifestations such as fever, malaise, sweating, hepatomegaly or splenomegaly [3, 9, 10, 26]. Routine laboratory data reported in most studies have been of little diagnostic value [19, 27].

Brucellosis often results in complications, in which the musculoskeletal system is most commonly affected [1, 9, 10, 15–17, 19]. Infection of the joints is the most frequent localised complication of brucellosis and a common cause of infectious arthritis in countries where the disease is endemic [4].

Musculoskeletal involvement is seen as the most frequent complication of brucellosis; however, its prevalence may vary from 0% to 70% [9, 10, 12, 19, 25, 28]. The diversity of criteria used

for the diagnosis of musculoskeletal involvement in brucellosis may cause variations in the results obtained by different researchers. In our study the ratio of patients with musculoskeletal complications of brucellosis (65%) was very high.

Brucellosis may also affect the musculoskeletal system at any site [3, 10, 24]. 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, 28]. Sacroiliitis usually occurs unilaterally in young people. In our study unilateral sacroiliitis (73%) was very common. However, Tasova [19] and Corderro-Sanchez [29] have found a high rate of bilateral sacroiliitis (47% and 60% respectively). In countries where infection with *B. melitensis* predominates, the sacroiliac joint is the most frequently involved musculoskeletal site [30]. Such involvement affects patients of all ages and may be associated with spondylitis in the elderly [1].

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, 28, 31, 32]. In our series, peripheral arthritis was the second most frequent type of musculoskeletal involvement. However, the rate of peripheral arthritis (54%) was higher than in other studies. The findings in other studies were 14–19.5% [3, 9, 19, 30].

On the other hand, the incidence of spondylitis reported in the literature varies significantly, ranging from 6% to >50% [1, 3, 12, 28]. The lumbar segment is by far the most commonly affected in patients with spondylitis, followed by the dorsal and cervical segments [33, 34]. Brucella spondylitis usually affects persons in the fourth to sixth decades of life [25, 34–37]. The mean age of the patients with spondylitis in our study was 44.56 ± 15.32 years. The rate of spondylitis was 31%, that of spondylitis in childhood (4%) and the elderly (12%) being slightly lower than in adults in the 195 patients (18%). However, of 39 elderly patients, 23 (68%) had spondylitis.

It is well known that radiographic abnormalities develop later on in the course of brucellosis with musculoskeletal complications, and that they are rare in peripheral arthritis [12, 28, 38]. Radiological findings of sacroiliitis within 2 or 3 weeks are blurring and indistinctness of the subchondral osseous line, narrowing and widening of the interosseous line and narrowing and widening of the interosseous space [30]. In spondylitis, the earliest radiographic finding is epiphysitis of the anterosuperior angle of the vertebra. During the progression of the disease, narrowing of the disc space, erosion, sclerosis, vertebral collapse and osteomyelitis may occur [25, 38, 36]. On the other hand, bone scintigraphy is not of great use in determining the outcome of brucellar musculoskeletal involvement, because abnormal uptake persists for a long time [9, 30]. In this study 117 (60%) of 195 patients had radiographic abnormalities at diagnosis, a figure similar to that reported by other studies [9, 19, 25, 28, 32]. Radiographic findings noted in spondylitis were similar to those found by other authors [9, 19, 28]. Involvement of the interapophysial joints, though scarcely reported previously, seemed to be fairly common. The presence of paravertebral or epidural abscesses, or both, is another unusual finding in many series [16, 19, 25, 36]. The high percentage found by us (23%) and other authors (16.6–37.5%) [9, 12, 39] may perhaps be related to the accuracy of the diagnostic criteria and the use of MRI and computed tomography, much more sensitive techniques than the conventional radiographic studies for the diagnosis of this complication.

In brucellosis, the aim of a treatment regimen is to control the acute illness and to prevent both complications and relapses. Most relapses occur within 3 to 6 months of discontinuing therapy. Treatment of patients should be prolonged, since the eradication of organisms from bone may be difficult. 6–8 weeks' combination therapy including rifampicin or streptomycin and doxycycline or tetracycline is recommended [40]. However, we believe at least 3–6 months' treatment would be beneficial in spondylitis and specific organ involvement such as carditis, osteomyelitis, prostatitis and meningitis. In this study we prefer therapy with rifampicin and doxycycline in cases with spinal involvement, as in our previous report [37]. Treatment with a single agent and of short duration carries a high risk of relapse [41]. We did not treat with a single agent or quinolone antibiotics, and thus our relapse rate was low (3.5%) during one-year follow-up in all patients.

In conclusion, in southeastern Anatolia musculoskeletal involvement in brucellosis is frequent. The main forms of this involvement are sacroiliitis, peripheral arthritis, and spondylitis in all age groups respectively. The present series suggests that musculoskeletal involvement in 15–45-year-olds is higher than in other groups. The prevalence of musculoskeletal involvement seems to vary according to age, sex, and clinical type. Musculoskeletal complications of brucellosis are important in view of their marked prevalence and also the associated functional disability. Hence, education of the public and government control in the area of preventive medicine are necessary to eradicate the disease. In particular, education of primary health care physicians should be promoted, given the fact that in Turkey most brucellosis patients are first seen and treated by these physicians.

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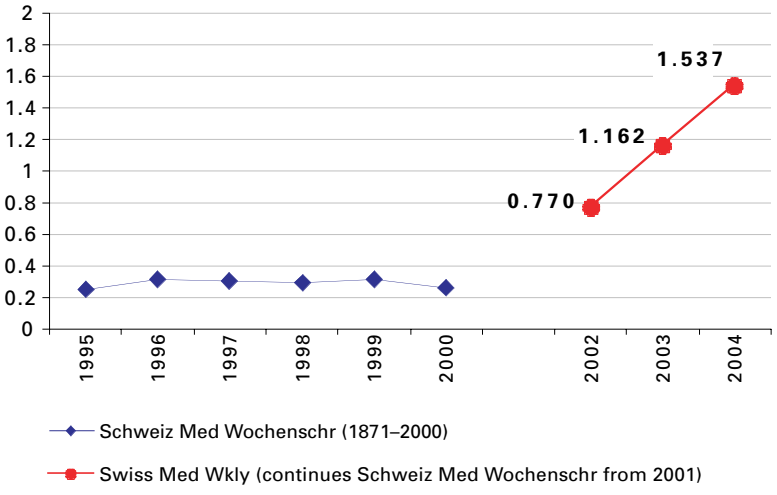

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