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Osteoarticular Involvement in Brucellosis: Study of 196 Cases in the Republic of Macedonia

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Aim. To describe the frequency, types, clinical characteristics, diagnostic tools, and outcome of osteoarticular brucellosis.

Methods. The study was carried out at the Hospital for Infectious Diseases in Skopje between January 1998 and December 2002. Three hundred and thirty one consecutive patients with brucellosis were enrolled and prospectively assessed according to a previously designed protocol. Brucellosis was diagnosed on the basis of clinical signs, and confirmed by the detection of specific antibodies at significant titers.

Results. One hundred and ninety six (59.2%) patients had osteoarticular involvement. Peripheral arthritis was found in 119 (60.7%) patients, followed by sacroiliitis in 60 (30.6%) and spondylitis in 56 (28.6%) of them. In 86 (43.9%) patients, osteoarticular changes were localized in two or more sites. The patients with osteoarticular brucellosis showed more prolonged illness prior to diagnosis and higher erythrocyte sedimentation rate, compared to those without osteoarticular localization. There were no other significant demographic, epidemiological, clinical, and laboratory differences between the two groups. Relapses occurred in 28 (17.5%) and therapeutic failure in 25 (12.8%) patients, 24 of them with spondylitis.

Conclusions. Osteoarticular brucellosis was a common form of focal brucellosis and the most unfavorable outcome was seen in patients with spondylitis.

Key words: *arthritis; brucellosis; musculoskeletal system; sacroiliac joint; spondylitis; recurrence*

Brucellosis is a severe public health and socioeconomic problem in many countries throughout the world. This disease is one of the most frequent zoonoses in the Mediterranean region and, in spite of the measures undertaken to prevent and control it, the incidence in some countries is still too high (1,2). The Republic of Macedonia (2.000,000 population) represents an endemic area where brucellosis prevails as a dominant zoonoses, and is the cause for high morbidity and huge economic loss. During the period between 1980-2002, a total of 9,041 cases of human brucellosis were reported (400-600 cases per year) (2,3). Geographical location, nomadism, overcrowding, husbandry practices, slaughtering, food, living habits, and trade are all risk factors allowing such a distribution of the disease (4). Brucellosis control program is not always based on obligatory test-and-slaughter of infected animals, and unsatisfactory compensations to the farmers whose herds are slaughtered do not improve the situation.

Human brucellosis is a systemic infection that can involve any organ or system of the body (5). In addition to the forms characterized by the multitude of somatic nonspecific complaints, such as fever, sweats, anorexia, fatigue, weight loss, symptoms and signs related to a single system occasionally predominate, when the disease is localized (5).

The most commonly localized form of human brucellosis is osteoarticular form (5-10). Osteoarticular brucellosis was documented by Marston (11) in 1861 at the time when this disease had not even existed as a separate entity. In the following decades, Marston's observation was supported by Bruce (12) and Hughes (13). It is an important entity because of its high prevalence and associated functional sequel (14). In addition to neurobrucellosis, osteoarticular form is the main cause of morbidity in brucellosis (15).

We analyzed the frequency, types, clinical characteristics, diagnostic possibilities, and outcome of osteoarticular brucellosis in the Republic of Macedonia.

Patients and Methods

Patients

The study was carried out at the University Hospital for Infectious Diseases and Febrile Conditions in Skopje between January 1998 and December 2002. Consecutive patients with brucel-

losis (n=331) were enrolled and prospectively monitored in order to study the osteoarticular form of the disease during its initial phase.

Diagnosis of Brucellosis

Brucellosis was diagnosed on the basis of the clinical presentation compatible with brucellosis (arthralgia, fever, sweating, malaise, hepatomegaly, splenomegaly, signs of focal disease), confirmed by the detection of specific antibodies at significant titers and/or demonstration of an at least fourfold rise in antibody titer in serum specimens obtained 3 to 4 weeks apart. Significant titers were determined to be Standard Tube Agglutination test (SAT) ≥1/160 and anti brucella Coombs test ≥1/320. The serological tests were performed according to techniques described previously (16,17). A suspension of *Brucella abortus 99* Weybridge strain (Biomerieux, Charbonnaires les Bains, France) was used as the antigen for the serological tests. Bacteriological isolation of *Brucella sp.* is still not common practice in the Republic of Macedonia.

Patients' Data

In all patients demographic, clinical, and laboratory data were recorded. The following laboratory parameters were examined: erythrocyte sedimentation rate (ESR), complete blood count, and blood chemistry profile. Rheumatoid factor (RF), antistreptolizin-O (AST-O), antinuclear antibodies (ANA), C-reactive protein (CRP), and circulating immune complexes (CIC) were also examined (when possible) in most patients.

A radiographic study of the spine and both sacroiliac joints in the prone position, and another osteoarticular location were performed for each patient with suspicious symptoms and signs, except in 18 patients with peripheral arthritis, a patient with costochondral arthritis and 2 patients with tendinitis. If there was suspicion of epidural or paravertebral abscess, and if radiography and isotopic bone scan could not confirm the suspicion of brucellar spondylitis, computed tomography (CT) (Somatom AR. HP, Siemens, Erlangen, Germany) or magnetic resonance imaging (MRI) (Gyroscan, NT Compact Plus, Philips, Eindhoven, Netherlands) was performed. Radiographic and CT findings of spondylitis confirmed the presence of intervertebral disk involvement, epiphysitis of the antero-superior angle, vertebral body destruction, interapophysial involvement, paravertebral, or epidural abscess. Radiographic findings of sacroiliitis included the blurring of margins, joint space narrowing or widening, subchondral erosion or sclerosis; and for peripheral arthritis joint space narrowing or widening, subchondral erosion, sclerosis, and soft tissue swelling.

A radionuclide bone scan with technetium-99 methylene diphosphonate (Tc-99m) (Spect Gamma Camera, Signature, Siemens, Orlando, FL, USA) was performed in cases where clinical suspicion of deep osteoarticular location was evident. Criteria for the evaluation of the bone scans were qualitative rather than quantitative. Increased uptake in an affected site was considered to be positive. Patients suspected of having hip arthritis underwent ultrasound examination from the beginning of 2000. Positive findings were joint space widening or narrowing and joint effusion.

Osteoarticular involvement was considered to be present if there were some inflammatory signs (swelling, pain, functional disability, heat, and redness) in any peripheral osteoarticular location, and/or inflammatory pain (pain unrelieved with rest) in any deep osteoarticular location accompanied by radiographic and/or radionuclide bone scan evidence of abnormalities. Spondylitis was defined as inflammatory back pain and stiffness along with radiological and/or CT changes of the spine and/or positive radionuclide bone scan with Tc-99m. Sacroiliitis was diagnosed with a Fabere test or by direct pelvic compression, along with radiological changes of the sacroiliac joint or positive radionuclide bone scan with Tc-99m. Peripheral arthritis was defined as pain, tenderness, swelling, and limitation of movements of any joint other than the spine, sacroiliac, costovertebral, costochondral, or sternochondral joint. For confirmation of coxitis we used radiography and/or radionuclide bone scan with Tc-99m, and/or ultrasound examination. Bursitis and tendinitis were defined by a clinical proof of inflammation of bursa and tendon.

The therapy consisted of a 45-day oral doxycycline (Doxycyclin, Alkaloid, Skopje, Republic of Macedonia; 100-200 mg/day in patients ≥8 years), rifampin (Rifampicin, Alkaloid, Skopje, Republic of Macedonia; 600-900 mg/day in adults, 15-20 mg/kg/day in children) and trimethoprim/sulfamethoxazole (Primotren, Lek, Ljubljana, Slovenia; 160/800-320/1600 mg/day in adults, 10-12/50-60 mg/kg/day in children). After completion of this therapeutic protocol in the patients with spondylitis and therapeutic failure, the treatment continued with doxycycline for a period of 3-12 months. Treatment-related serious adverse effects included the withdrawal of the incriminating medicine and continuing the treatment with the other two remaining drugs. Pregnant women, breast-feeding mothers, and children aged up to 8 years were treated with the combination of rifampin and trimethoprim/sulfamethoxazole with doses and time duration stated above.

Follow-up

The patients were hospitalized until clinical improvement was achieved. Laboratory and serological controls were conducted on the 15th and 40th day of the treatment. In the next three months, these check-ups were done once a month, and then every 3-6 months. If necessary, controls were made in a period shorter than the anticipated if signs or symptoms of relapse appeared or if there was worsening of the existing signs and symptoms. In case of relapses, the same diagnostic and therapeutic procedures were performed as during the initial episode.

Outcome

Osteoarticular duration was assessed as the number of days that elapsed from the start of treatment until signs disappeared, and defervescence as the period from the start of therapy, until patients became afebrile. Therapeutic failure was defined as the persistence of disease symptoms and signs after the completion of a 45-day therapy, and relapse as the reappearance of disease symptoms and signs up to 12 months after the antibrucellar treatment was completed. Sequels were considered to have occurred when pain and/or functional disorders persisted longer than 6 months after the therapy. The severity of sequel was classified at the end of the follow-up as: (a) mild-pain present during exercise that did not interfere with work and (b) moderate/severe-permanent excruciating pain (requiring analgesics) and/or functional disorders which prevented the patient from his occupation or daily activities. Outcome was categorized as favorable (recovered with no or mild sequel) or unfavorable (relapse, therapeutic failure, moderate/severe sequel, or mortality). Relapses and sequels were evaluated only in patients who had a follow-up period of at least 6 months post-therapy, whereas therapeutic failure and mortality were estimated in all treated patients irrespective of the follow-up period.

Statistical Analysis

The patient's age, illness and arthritis duration, defervescence, and follow-up period were presented using median and range values. Chi-squared test with Yates' correction and Fisher exact test (when appropriate) were used for qualitative variables. For quantitative variables the comparison was performed using Student's t-test, Kruskal-Wallis test, and Mann-Whitney U test. P values <0.05 were considered significant. Statistical analysis was preformed using SPSS statistical package for Windows, version 12.0 (SPSS Inc, Chicago, IL, USA).

Results

The patients with brucellosis had a median age of 36 years (range 3-78). During the initial episode of illness, osteoarticular localization manifested in 196 out of 331 patients (59.2%). Other focal forms were hepatic (32.9%), genitourinary (11.2%), hematological (9.1%), pulmonary (6%), neurological (2.7%), and cardiovascular (1.2%).

More than half of the patients (172, 52.0%) came from families where brucellosis had been already recorded, and osteoarticular form was found in 93 (54.1%) of them, whereas 159 (48.0%) patients were the only cases that manifested this disease in their families and 103 (64.8%) of them had osteoarticular form. In 10 (3.0%) individuals osteoarticular affection

Table 1. Sites of involvement in 196 patients with osteoarticular brucellosis

Type of involvement	No. (%)
Spondylitis	35 (17.9)
Spondylitis + sacroiliitis	10 (5.1)
Spondylitis + sacroiliitis + peripheral arthritis	2 (1.0)
Spondylitis + peripheral arthritis	9 (4.6)
Sacroiliitis	29 (14.8)
Sacroiliitis + peripheral arthritis	19 (9.7)
Peripheral arthritis	82 (41.8)
Peripheral arthritis + bursitis	6 (3.1)
Peripheral arthritis + sternochondral arthritis	1 (0.5)
Costochondral arthritis	1 (0.5)
Tendinitis	2 (1.0)

Table 2. Distribution and rates of 172 peripheral arthritides in 119 patients with brucellar peripheral arthritis

	Arthritis (No.)		
Joint	unilateral	bilateral	Total (%)
Hip	45	1	46 (38.6)
Knee	34	4	38 (31.9)
Ankle	23	6	29 (24.4)
Shoulder	13	0	13 (10.9)
Elbow	6	0	6 (5)
Wrist	8	2	10 (8.4)
Sternoclavicular	9	1	10 (8.4)
Other*	4	1	5 (4.2)

*Temporomandibular and interphalangeal joints of the hands.

appeared during the treatment, and in other 8 (2.4%) it resolved before the diagnosis of brucellosis was established and treatment initiated.

Out of 196 patients 110 (56.1%) had osteoarticular changes localized to a single segment, and in 86 (43.9%) two or more sites were affected (Table 1).

Peripheral arthritis was the most common manifestation, found in 119 (60.7%) patients. There were 78 male and 41 female subjects at the median age of 30 (range 4-69) years. In 84 (70.6%) subjects, arthritis was manifested as monoarthritis and in 35 (29.4%) as olygo or polyarthritis (Table 2).

Sixty patients had sacroiliitis, which comprised 30.6% of the patients with osteoarticular form. The median age of the patients with sacroiliitis was 30.5 years (range 11-69). In 42 (70%) patients sacroiliitis was one sided and in 18 (30%) it was bilateral.

Spondylitis manifested in 56 (28.6%) patients. Thirty-three of them were male and 23 female. The

Table 3. Comparison of 331 patients with brucellosis with or without osteoarticular involvement

	No. (%) of patients		
Parameter	with osteoarticular brucellosis (n = 196)	without osteoarticular brucellosis (n = 135)	p
Male gender	126 (64.3)	97 (71.8)	0.186†
Age (years, median; range)	34 (4-76)	36 (3-78)	0.800‡
Illness duration prior to therapy (days, median; range)	30 (3-360)	30 (4-360)	0.001‡
Acquisition of illness:			0.699†
direct	110 (56.1)	71 (52.6)	
indirect	64 (32.7)	45 (33.3)	
unknown	22 (11.2)	19 (14.1)	
Temperature > 38°C	117 (59.7)	86 (63.7)	0.534†
Headache	108 (55.1)	80 (59.3)	0.524†
Arthralgia*	145 (74)	92 (68.1)	0.302†
Weight loss	51 (26)	30 (22.2)	0.509†
Malaise	133 (67.9)	88 (65.2)	0.698†
Sweating	149 (76)	90 (66.7)	0.082†
Hepatomegaly	101 (51.5)	66 (48.9)	0.718†
Splenomegaly	59 (30.1)	37 (27.4)	0.684†
Lymphadenopathy	61 (31.1)	39 (28.9)	0.754†
Other focal form	97 (49.5)	68 (50.4)	0.963†

*Pain in the joints without arthritis.
†Chi-square test with Yates' correction.
‡Student's t-test.

Table 4. Laboratory and serological data of 331 patients with brucellosis with or without osteoarticular involvement

	Patients		
Parameter	with osteoarticular brucellosis n = 196	without osteoarticular brucellosis n = 135	p
Erythrocyte sedimentation rate (mm/h, mean ± SD)*	37.0 ± 26.1	30.5 ± 22.2	0.015§
Hemoglobin (g/L, mean ± SD)	126 ± 17.6	128.3 ± 16.8	0.250§
White blood cells (× 109/L, mean ± SD)	6.8 ± 2.3	6.4 ± 2.2	0.120§
Lymphocytes (≥40%)†	74/188 (39.4)	54/132 (40.9)	0.871‡
Alanine aminotransferase (> 40 U/L)†	59/196 (30.1)	44/135 (32.6)	0.719‡
Circulating immune complex (> 0.05 g/L)†	149/176 (84.7)	92/102 (90.2)	0.260‡
Antistreptolysin O test (> 400 Todd U/L)†	2/167 (1.2)	4/106 (3.8)	0.211‖
C reactive protein (> 8 mg/L)†	120/162 (74.1)	76/98 (77.5)	0.630‡
Standard tube agglutination test (median; range)	640 (80-1280)	640 (80-1280)	0.119¶
Anti brucella Coombs (median; range)	1280 (160-1280)	1280 (160-1280)	0.368¶

*SD – standard deviation.
†No. of positive/No. of examined patients (%).
‡Chi-square test with Yates' correction.
§Student's t-test.
‖Fisher exact test.
¶Mann-Whitney U test.

median age of these patients was 55.5 (range 16-76) years. In 48 (85.7%) subjects one and in 8 (14.3%) multiple spinal levels were involved. The most affected spinal segment in 43 patients was the lumbar one, thoracic localization was found in 16, and cervical spondylitis in 6 patients. Paravertebral abscess was found in 4 patients – thoracic abscess in 3 and lumbar in 1 patient.

Sweating, arthralgia, and malaise were the most frequent complaints, whereas hepatomegaly was the commonest sign (Table 3). Patients with spondylitis showed longer duration of illness from the onset of the symptoms to its diagnosis (median 45; range 7-360 days), compared to those with sacroiliitis (median 30; range 7-300), peripheral arthritis (median 30; range 3-360), and non-osteoarticular brucellosis (median 30; range 4-360) ($p < 0.001$). Also, as mentioned above, patients with spondylitis were older than those with sacroiliitis, peripheral arthritis, and non-osteoarticular brucellosis ($p < 0.001$).

There were no significant laboratory and serological differences between the groups with and without osteoarticular brucellosis during the initial examination, except higher erythrocyte sedimentation rate in the osteoarticular group (Table 4). Elevated circulating immune complexes and C-reactive protein were the dominant laboratory characteristics. Platelets count and uric acid levels were within the normal range in all patients. All were antinuclear antibodies negative and had rheumatoid factor < 1/40. Twenty-eight cases had a significant increase in anti brucella Coombs titer of serial samples.

Synovial fluid was analyzed in 18 cases. Mean white cell count was $12.6 \pm 7.5 \times 10^9$/L (range 2.6-23.2×10^9/L), with lymphocytosis of 41.1 ± 18.1% (range 14-69%). Glucose, protein, and lactic acid content were with mean value of 3.3 ± 2.2 mmol/L (range 1.2-7.9 mmol/L), 50.4 ± 17 g/L (range 39-88 g/L) and 6.2 ± 3.3 mmol/L (range 2.2-13.1 mmol/L), respectively. None of the synovia aspirates showed organisms on Gram stain.

Radionuclide bone scan was performed in 127 patients and was positive in 116 (91.3%) of them (Table 5). The scan was positive in 81 osteoarticular locations with no radiological abnormalities: 7 spinal, 34 sacroiliac, and 40 peripheral. CT and MRI were done in 38 and 6 patients, respectively. They were especially useful in diagnosis of spondylitis with paravertebral abscess and in follow-up its evolution.

The median defervescence occurred for 3 (range 1-21) in osteoarticular and 3 (range 1-21) days in non-osteoarticular group ($p = 0.106$). The median defervescence in patients with spondylitis, sacroiliitis, and peripheral arthritis was 5 (range 1-21), 4 (range 1-21), and 3 (range 1-21) days, respectively. The median duration of spondylitis was 105 (range 30-360) days, sacroiliitis 30 (range 10-60), and peripheral arthritis 14 (range 4-45) days.

Patients with osteoarticular involvement were followed-up for median 10 (range 2-70) and patients without it for median 8 (range 1-70) months ($p = 0.105$). In 36 and 24 patients out of 196 and 135 with and without osteoarticular brucellosis respectively, the follow-up period lasted less than 6 months and they were excluded from the evaluation of relapses and sequels. Twenty-eight patients with osteoarticular brucellosis manifested a relapse (Table 6). The response to re-treatment was favorable in 25 patients. Hitherto, two patients had two and one even three relapses, all of them with favorable outcome. Therapeutic failure occurred in 25 patients with osteoarticular brucellosis; 24 had spondylitis, and 8 of them had concomitant osteoarticular localization (Table 6). Moderate sequel occurred in 8 subjects, all with therapeutic failure. Sequel comprised of spinal pain in 4, functional disability in 3, and hip ankylosis in one patient. Another patient with spondylitis developed renal failure as well as hypostatic pneumonia and died. Not one of the patients was subjected to sur-

Table 5. Radiographic findings at 285 sites in 175 patients with osteoarticular brucellosis*

Site/type	No. (%) of patients	No. (%) of osteoarticular sites
Spondylitis:	56	65
disk involvement	32 (57.1)	36 (55.4)
anteosuperior epiphysitis	32 (57.1)	34 (52.3)
vertebral body destruction	25 (44.6)	28 (43.1)
interapophysal involvement	6 (10.7)	6 (9.2)
paravertebral abscess	4 (7.1)	4 (6.2)
no changes	5 (8.9)	7 (10.8)
Sacroiliitis:	60	78
poorly defined joint margins	13 (21.7)	15 (19.2)
sclerosis	12 (20.0)	13 (16.7)
joint space narrowing	8 (13.3)	8 (10.3)
joint space widening	5 (8.3)	6 (7.7)
subchondral erosion	4 (6.7)	5 (6.4)
no changes	22 (36.7)	34 (43.6)
Peripheral arthritis:	101	142
joint space narrowing	4 (4.0)	4 (2.8)
joint space widening	11 (10.9)	11 (7.7)
subchondral erosion	6 (5.9)	6 (4.2)
sclerosis	5 (5.0)	5 (3.5)
soft tissue swelling	5 (5.0)	5 (3.5)
no changes	70 (69.2)	111 (78.2)

*Radiographic examination was performed in 175 of 196 patients with osteoarticular brucellosis.

Table 6. Outcome in patients with brucellosis

Outcome	No. (%) of patients with osteoarticular brucellosis	No. (%) of patients without osteoarticular brucellosis	p
Relapse*	28/160 (17.5)	17/111 (15.3)	0.757‖
Therapeutic failure†	25/196 (12.8)	5/135 (3.7)	0.009‖
Mortality‡	1/196 (0.5)	0/135	
Moderate/severe sequel§	8/160 (5)	2/111 (1.8)	0.206

*No. of the patients with relapses/No. of the patients followed-up for at least 6 months post-therapy.
†No. of the patients with therapeutic failure/No. of the patients who completed the treatment.
‡No. of deaths/No. of the examined patients.
§No. of the patients with sequel/No. of the patients followed-up for at least 6 months post-therapy.
‖Chi-square test with Yates' correction.
¶Fisher exact test.

gery, including 4 patients with paravertebral abscess. When using prolonged antimicrobial therapy with doxycycline all the patients showed abscess restitution.

Discussion

This study assessed one of the largest group of patients with osteoarticular brucellosis published in literature. In spite of the technical difficulties, like the lack of bacteriological diagnostics, and problems in performing expensive diagnostic procedures (polimerase chain reaction, humane leukocyte antigen [HLA] complex, magnetic resonance imaging), this study provides important data for this form of the disease in an endemic region.

There have been large discrepancies in the reported frequency of osteoarticular brucellosis as well as on the most affected osteoarticular structures. The prevalence of osteoarticular involvement varies in a range from 2 to 85% depending on the source of information (6,9,14,18-32). Still, in majority of reports it ranges from 20-40% (9,14,19,20,27,31). Our frequency of 59.2% is among the highest mentioned in literature (30,32).

The reported frequency of peripheral arthritis ranges from 15 to 78% (9,20,21,23,24,32, 33). It was the most common form in this report, with the obviously commonest localization on the large joints of the lower extremities. Although one of peripheral arthritis characteristics is predominance in children and young adults (19,34), we found that it was also frequent in middle-aged group and even one third showed oligoarthritis. Ten patients (5.1%) had sternoclavicular arthritis, making it the highest frequency ever reported for brucellosis (35,36).

Brucellar sacroiliitis was reported in 0 to 72% of the patients with osteoarticular brucellosis (7,9,19, 20-24,27,28,33,37,38). It was mainly unilateral in more than 80% of the patients (9,14,19,24,27,32,39). However, we registered unilateral sacroiliitis in 70% of the patients. Although predominant in young adults in some investigations (19,26,40), the age characteristics of patients in the Republic of Macedonia did not differ from those reported by Ariza et al (39).

The reported prevalence of brucellar spondylitis ranges from 2.9 to 65% (9,14,19-24,27-29,33,38,41). Spondylitis was most frequent in older patients (14, 27,29,31,42-44) and patients with longer illness duration before establishing diagnosis (19).

Explanations for the discrepancies in the frequency and distribution of osteoarticular brucellosis are certainly due to several factors, including the characteristics of the examined population, the nature of the causative agent, possible geographic variations of the disease, stage of the disease, diversity of applied criteria for defining the cases, used diagnostic procedures as well as the lack of sufficient prospective studies (9,14,20-23,26,27,29-31,37,38,43-46). We registered high prevalence of simultaneous osteoarticular involvement in various combinations. Almost half (44%) of our patients demonstrated multiple osteoarticular localization. We think that the long interval before establishing the diagnosis is a result of a delayed referral to the hospital, rather than not recognizing the disease. Like Colmenero et al (14), our patients with osteoarticular brucellosis showed longer diagnostic delay compared with the patients without osteoarticular localization. This probably resulted in higher prevalence of osteoarticular involvement, and also in frequent simultaneous affection of more osteoarticular structures.

Similar to Gotuzzo's et al (20), our series had many patients who were from the same family. We have also confirmed his observation that osteoarticular brucellosis occurred less frequently in individuals with brucellosis in their family, probably because family cases could be diagnosed and treated earlier.

In 18 patients, antibrucellar treatment had no influence on joints manifestations, indicating reactive arthritis. All six who were tested for HLA-B 27 were negative, similar to other reports (8,24,47-49).

Hematological and laboratory parameters and biochemical analysis of synovial fluid showed various discrepancies, and were inconclusive for the diagnosis of brucella arthritis. In some reports, synovial cultures remained negative (9,21,27), whereas in some others the rate of isolation of *Brucella sp* was low (19). Our experience is that synovial puncture is neither diagnostic nor therapeutic routine procedure in endemic regions and should be done only on occasions when there is suspicion of gout or pseudo gout, or when there is no response to therapy.

Radiological examinations, although not an especially sensitive diagnostic method for extraspinal localization (9,14,21,41,46), remain being an important instrument for determining osteoarticular brucellosis. These examinations are supplemented with a radionuclide bone scan, despite of the fact that it has low specificity (15,50), it is not a good modality to show soft tissue abnormality (51,52) and it is not useful in determining the course of illness because abnormal uptake persists for a long time (14,25,32,39). In this study radionuclide bone scans were positive in 81 locations (mainly extraspinal) where radiography was normal. In less developed countries where MRI is not always accessible, the basic procedure for confirming deep osteoarticular location in brucellosis should be radiography, combined with radionuclide bone scan. Small number of paravertebral and no epidural abscesses reported in our study are maybe a result of a small number of MRI performed, even though we found references with significantly higher percentage of abscesses, without employing this diagnostic procedure (14,31,42,53). Using MRI some authors found soft tissue masses from 0 to 89% in patients with brucellar spondylitis (25,32,44).

Therapeutic response measured through defervescence and duration of arthritis was satisfactory in the majority of patients without spondylitis. The number of relapses was high, although we observed no variations between the groups with and without osteoarticular involvement, which is disparate to some prior findings (41,54). Possible reasons for high percent of relapses found in some studies could be: agent virulence, the inability to distinguish re-infec-

tions, bad compliance, not completely adequate choice of antibiotics, short treatment duration, or the prospective nature of the studies (7,9,14,27,41,46, 54-56).

It is well known that brucellar spondylitis is often associated with therapeutic failures (14, 31,44,56, 57). Some other focal forms and probably geographical distribution of the disease could also be associated with therapeutic failures (21,23,25,27,31,43, 56). Because of that antimicrobial therapy in brucellar spondylitis should be prolonged. Unfortunately, there is no consensus about the best antimicrobial combination and treatment duration. Surgical intervention is the last resort in the management of spinal brucellosis and is advised only when there is persistence or progression of neurological deficits caused by soft tissue masses, progressive vertebral collapse, spinal instability, or when there is no response to prolonged antibiotic treatment (14,43,58,59). Moderate and severe sequel are rare events in osteoarticular brucellosis (31,39,41,44,46,58) and mortality an exceptional one (42,58).

In conclusion, osteoarticular brucellosis is still a common focal form of the disease in the Republic of Macedonia. Each patient with rheumatoid symptoms should be considered for brucellosis. Special attention should be paid to the detection and treatment of brucellar spondylitis, as it is the major reason for therapeutic failures and sequels. Measures targeted to inactivate the pathogenic power of the agent (ie milk pasteurization) and measures targeted to change behaviors at risk such as health education and information are essential for the prevention of human brucellosis (60).

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