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# Hip arthritis in brucellosis: a study of 33 cases in the Republic of Macedonia (FYROM)

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## SUMMARY

Prospectively were studied clinical characteristics, diagnostic tools and outcome in 33 patients with hip arthritis during brucellosis that were treated at the clinic for infectious diseases in Skopje, Republic of Macedonia (FYROM). Thirty-six hip involvements were noted. The patient's age was mean (SD) 23.7 (19.9) years, 18 were male. Twenty-one of them acquired the disease through direct contact with infected animals. In five patients, hip arthritis was the unique manifestation of the disease. Concomitant

affection of other osteoarticular localisation was found in 18 patients. The diagnosis of hip arthritis was achieved using radionuclide bone scan and ultrasound examination in 17 and 16 cases, respectively. During the follow-up period, six relapses, three therapeutic failures and one sequela were noted. Brucellar aetiology should be considered in all patients from endemic areas, who have manifest symptoms of hip joint involvement.

**Keywords:** Arthritis; brucellosis; hip

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## INTRODUCTION

Brucellosis imposes a serious public health and socio-economic problem in many Mediterranean countries (1,2). With an incidence of  $\geq 20$  per 100,000 inhabitants, this disease is the most common zoonosis in the Republic of Macedonia (FYROM) (3). Human brucellosis is a systemic infection that can involve any organ or system of the body (4). The most commonly localised form is osteoarticular one (5–7). It is an important entity because of its high prevalence and associated sequelae (8). Hip arthritis sometimes is a constituent segment of brucellosis; however, it has not received enough attention, yet.

Our aim was to present in a prospective study, demographic, clinical and laboratory characteristics, diagnostic possibilities and outcome of patients suffering from brucellar hip arthritis in the Republic of Macedonia (FYROM).

## MATERIALS AND METHODS

Thirty-three patients with hip arthritis were prospectively analysed, of a cohort of 263 patients with brucellosis treated at the clinic of infectious diseases and febrile conditions in Skopje (university hospital with 130 beds) in the period between March 1998 and August 2002.

Brucellosis was diagnosed on the basis of clinical picture compatible with brucellosis (fever, sweating, malaise, arthralgia, hepatomegaly, splenomegaly and signs of focal disease), supported by detection of specific antibodies at significant titres and/or demonstration of at least four-fold rise in antibody titre in serum specimens obtained 3–4 weeks apart. Significant titres were determined to be standard tube agglutination test (SAT)  $\geq 1/160$  and anti-brucella Coombs test  $\geq 1/320$ . The serological tests were performed according to techniques described previously (9,10). A suspension of brucella abortus 99 Weybridge strain (Biomerieux, Charbonnieres les Bains, France) was used as antigen for the serological tests. Bacteriological isolation of *Brucella* sp. in Republic of Macedonia is not employed in practice.

All patients were assessed prospectively according to previously designed protocol, which included demographic, clinical and laboratory data. The following laboratory parameters were examined: erythrocyte sedimentation rate, complete blood count, blood chemistry profile, rheumatoid factor, anti-streptolysin-O, C-reactive protein and circulating immune complexes. A radiographic study of all suspected hip involvements was performed. Radiographic abnormalities in hip arthritis were joint space narrowing or widening, subchondral erosion, subchondral sclerosis and/or soft tissue swelling. A radionuclide bone scan with technetium<sup>99m</sup> methylene diphosphonate was performed, when clinical suspicion for hip involvement was strong. Criteria for evaluation of the bone scans were qualitative rather than quantitative. Increased uptake in the hip was considered to be positive. A number of patients underwent ultrasound examinations of affected hips since the beginning of the year 2000. Positive findings were joint space widening or narrowing and joint effusion.

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Hip arthritis was defined as pain, tenderness and limitation of movement, confirmed with radiographic and/or radionuclide bone scan with technetium<sup>99m</sup> methylene diphosphonate and/or ultrasound abnormalities.

Therapeutic protocol consisted of doxycycline (100–200 mg/day), rifampin (600–900 mg/day adults, 15–20 mg/kg/day children) and co-trimoxazole (960–1920 mg/day adults, 10–12/50–60 mg/kg/day trimethoprim/sulfamethoxazole children) per oral administration in time duration of 45 days. Children aged up to 8 years were treated with combination of rifampin and co-trimoxazole.

The patients were hospitalised until clinical improvement. Laboratory and serological controls were conducted 15th and 40th day, since the beginning of the treatment. In the next 3 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 planned. In case of relapses, the same diagnostic and therapeutic procedures as when the initial episode had happened were performed.

Hip arthritis duration was assessed as the number of days elapsed from the start of treatment until movements completely restored and ultrasound abnormalities 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 completion of 45 days therapeutic course, and relapse as the reappearance of disease symptoms and signs up to 12 months after the anti-brucellosis treatment was completed. Sequelae were considered to have occurred when permanent excruciating pain (requiring analgesics) and/or functional and/or anatomic disorders, which prevented the patient from his occupation or daily activities, persisted for longer than 6 months post-therapy. Outcome was categorised as favourable (recovered) or unfavourable (relapse, therapeutic failure or sequelae).

The  $\chi^2$  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. Differences for *p* values <0.05 were considered significant.

## RESULTS

Two hundred and sixty-three patients with brucellosis were analysed. Hip joint involvement was present in 33 (20.4%) of 162 patients with osteoarticular form of the disease. Hip arthritis was manifested as primary attack in 32 individuals, whereas in one, it presented during a relapse. There were 36 episodes of hip joint involvement in these 33 patients (bilateral coxitis in one and re-affected of the same hip during the relapse in two other patients).

The age of the subjects with hip arthritis was mean  $\pm$  SD 23.7  $\pm$  19.9 years (range 4–69). Eleven of them were under

10 years of age. There were 18 male and 15 female. In 21 of them, the disease was acquired through direct contact with infected animals, and in 10, it was caused by ingestion of incriminated products whereas in two patients, the origin was unknown. The single significant difference between the patients with hip arthritis and those without it, according to demographic characteristics, was their age; patients with hip arthritis were younger than the other population with brucellosis (mean  $\pm$  SD 39.7  $\pm$  18.2 years) (*p* < 0.001).

The time between the onset and diagnosing the disease was 43.8  $\pm$  44.5 (range 5–180) days. Hip arthritis appeared 12.2  $\pm$  7.3 (range 5–25) days prior to diagnosing brucellosis, except for two patients who manifested it during the treatment period. In 21 individuals, the onset of hip arthritis was after the appearance of the general symptoms, in four it occurred before their manifestation, in three coxitis appeared simultaneously with the other symptoms whereas in five patients, it was manifested without other signs and symptoms for the disease.

As summarised in Table 1, the most frequent complaint in patients with coxitis was arthralgia that does not refer to pain in affected hip, whereas hepatomegaly was the most common sign. 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. None had rheumatoid factor >1/40, and two older patients showed anti-streptolysin-O titre >400 Todd U/l.

Eighteen patients had concomitant affection of other osteoarticular localisation: two had spondylitis, five sacroiliitis, two sternoclavicular arthritis, one radiocarpal bursitis and eight patients had some other peripheral arthritis.

Hip arthritis occurred on the left side in 14 and on the right side in 22 cases. Intense pain was present in 15 cases, it was moderate in 16, and mild in five hip joints affections. In 17 cases, the pain did not radiate whereas in 19 cases, it radiated in 10 in one direction and in the remaining nine, it was directed towards several sites. The pain radiated towards the thigh in 13 cases, in nine, it spread in the inguinal region, and in six cases, there were sciatic pains. Adduction and internal rotation was not possible in 33 cases with hip arthritis each, whereas in 25, 21, 18 and 17 cases, there was compromised extension, flexion, abduction and external rotation, respectively.

Diagnosis of hip arthritis was established with ultrasound in 15 cases, with radionuclide bone scanning in 14 and with plain radiography in four. In the remaining three cases, different combinations of the diagnostic methods were used, including magnetic resonance imaging (MRI) (Table 2). Plain radiographs with positive findings revealed widening of the osteoarticular space in three, subchondral sclerosis in two and erosions in one case. In 10 cases, ultrasound examination showed effusion, and in the rest, there was widening of the osteoarticular space.

**Table 1** Signs, symptoms, laboratory and serology analyses in 33 patients with hip arthritis during brucellosis\*

Parameter	Number of patients
Temperature	22
Perspiration	22
Arthralgia†	27
Malaise	16
Headache	18
Weight loss	4
Hepatomegaly	15
Splenomegaly	9
Lymphadenopathy	8
Other non-osteoarticular localisation	13
Erythrocyte sedimentation rate	
≥40 mm/h	17
Haemoglobin	
≤100 g/l	5
Red blood cell	
≤3500 × 10 <sup>12</sup> /l	3
≥5500 × 10 <sup>12</sup> /l	1
White blood cell	
≤4 × 10 <sup>9</sup> /l	4
≥10 × 10 <sup>9</sup> /l	2
Lymphocytes	
≥40%	9
Alanine aminotransferase	
>40 U/l	9
Circulating immune complexes‡	
>0.05 g/l	24
C-reactive protein	
>8 mg/l	23
Standard tube agglutination test	
≤160	6
320	4
640	8
≥1280	15
Anti-brucella Coombs	
≤160	3
320	4
640	5
≥1280	21

\*No significant difference in the presented characteristics compared with the patients without coxitis. †Does not refer to pain in affected hip. ‡Of 31 patients.

Therapeutic approach in 26 patients consisted of doxycycline/rifampin/co-trimoxazole and in seven of rifampin/co-trimoxazole. Additional therapeutic courses were followed in nine patients: in four doxycycline/rifampin/co-trimoxazole and in two rifampin/co-trimoxazole were applied. Three

patients received prolonged treatment with doxycycline for the period of 3–12 months, due to therapeutic failure.

The patients were followed-up for 12.3 ± 10.9 (range 2–60) months. The follow-up period was shorter than 6 months in two subjects, and they were not included in the assessment of the disease outcome.

Defervescence period lasted for 3.1 ± 4.7 (range 0–18) days. A total of 22 patients were cured with the first therapeutic course. Relapse appeared in six and therapeutic failure in three patients. Three of the subjects suffering a relapse had oligoarthritis and one concomitant sacroiliitis during the first episode. In the therapeutic failure group, two patients had concomitant spondylitis and one had oligoarthritis. Sequela (hip ankylosis) was noted in a 63-year-old female, who had implanted endoprosthesis of the right hip after a trauma, 3 years prior to brucellosis onset. If we exclude this patient, coxitis duration was 23.1 ± 15.3 (range 7–90) days. No significant difference was found between the patients with and without hip arthritis, concerning defervescence and parameters those determine outcome.

## DISCUSSION

Hip joint involvement is one of the most common osteoarticular manifestations of human brucellosis (5,11–13). In some examined series, the frequency ranges within a scope of 18–60% among the patients with osteoarticular brucellosis (5,7,12,14,15). The cause of this high frequency rate of coxitis during brucellosis is unknown. It is most probably due to the function (12) as well as to precarious blood supply (14), although the fact of unilateral affection, which was found in all of our patients except one, raises doubts for such an explanation.

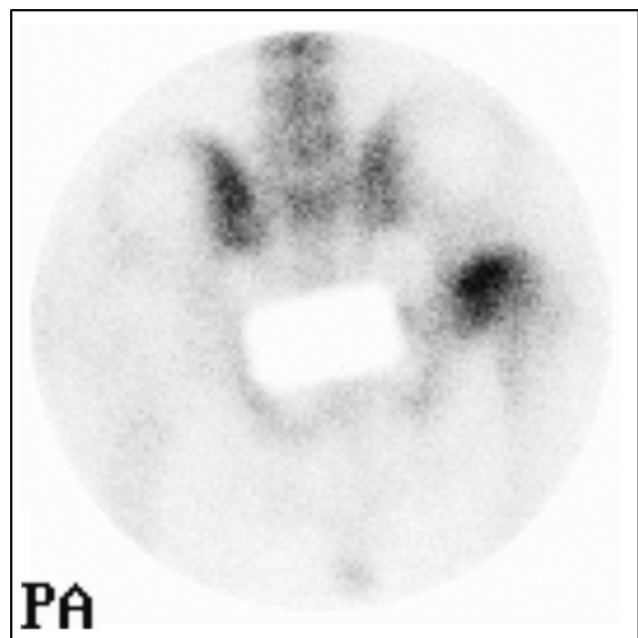
In spite of the high frequency and sometimes serious condition of the patients with brucellar hip arthritis prior to and some time from the beginning of its treatment, this entity has not raised enough interest recently. Over the last several decades, there have not been any published articles analysing the characteristics of coxitis in the general population with brucellosis, except for the communications for brucellar hip arthritis in childhood (14) and separate rare peculiar cases, such as infections in artificial hip prosthesis (16,17) and brucellar coxitis as well as avascular necrosis of the femoral head (18). These were the reasons why we decided to present our experience with hip arthritis during brucellosis in patients from the Republic of Macedonia (FYROM).

**Table 2** Diagnostic procedures in patients with brucellar hip arthritis

Diagnostic procedure	Times performed	Positive finding
Plain X-ray	36	6
Radionuclide bone scan with technetium <sup>99m</sup> methylene diphosphonate	20	17
Ultrasound	16	16
Magnetic resonance imaging	1	1

We noted high concomitant association of coxitis and other osteoarticular involvements, the fact already noticed but never enough emphasised (14,19,20). We consider that long diagnostic delay could be the reason for such a high per cent of multiple osteoarticular involvement, which according to our experience often results in unfavourable outcome. Even four of six relapses and all therapeutic failures were in patients with concomitant osteoarticular involvement.

Pain characteristics and physical examination cannot always differentiate hip arthritis from sacroiliitis in brucellosis (14). Therefore, it is necessary to add adequate investigation in order to make correct diagnosis. Radionuclide bone scan (Figure 1) and ultrasound examination (Figure 2) are sovereign methods for hip arthritis confirmation. Isotopic scan investigations in osteoarticular brucellosis have been described elsewhere (21–23). The advantage of radionuclide bone scan is in its possibility of easy differentiation of coxitis from sacroiliitis (12), still, it is not useful in determining the course of illness because abnormal uptake persists for a long time (2,8,21). Moreover, in three occasions, it was false negative and in these cases, ultrasound confirmed presence of hip arthritis. Ultrasound examination is quick, reliable, offer comfort to the patient as well as immediate inspection of the affected hip (24,25). Our series contains the biggest number of reported hip arthritis in brucellosis that were diagnosed using this method. This enables us to suggest that ultrasound is the most preferable method for diagnosing and especially monitoring of brucellar coxitis, which often allows avoidance of radiological and scintigraphic examination. In contrast, plain radiography has not proved to be susceptible diagnostic method. Perhaps, this is due to its early performance at the



**Figure 1** Radionuclide bone scan with technetium<sup>99m</sup> methylene diphosphonate in brucellar hip arthritis: increased uptake



**Figure 2** Ultrasound examination in brucellar hip arthritis: widening of the articular space and effusion

time when changes cannot still be verified by radiographic examination (21,26). MRI is rarely available diagnostic tool in developing countries where brucellosis presents a health problem.

As tuberculosis testing and vaccination is obligatory in childhood and adulthood in the Republic of Macedonia (FYROM), we rarely consider tuberculosis as a cause of hip arthritis. Lyme disease is excluded using clinical characteristics and serological tests, as well as rheumatic fever and systemic lupus erythematosus, whereas usually, normal leukocytes and granulocytes count helps us to exclude pyogenic hip arthritis. Some other conditions that can cause coxitis, such as juvenile rheumatoid arthritis, reactive arthritides due to enteric bacteria, gout or other rare genetic syndromes, were always taken into consideration. Careful clinical evaluation and follow up as well as usually satisfactory response to anti-brucellar treatment had priority in excluding these conditions.

In conclusion, a brucellar aetiology should be considered in all patients in the Republic of Macedonia (FYROM), who have manifest symptoms of hip joint involvement. If there is clinical suspicion, ultrasound should be the method of choice for coxitis confirmation. Early recognition, adequate treatment and monitoring in the majority of cases are a guarantee for successful outcome.

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