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Original Article

Can imaging modalities be used as follow-up criteria after brucellar sacroiliitis treatment?

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Abstract

Introduction: This study aimed to identify a follow-up modality that can be used to evaluate therapeutic responses in patients receiving treatment for brucellar sacroillitis and to determine whether antibiotherapy can be stopped.

Methodology: A total of 32 patients with sacroiliac joint involvement demonstrated via magnetic resonance imaging or bone scintigraphy were followed up and treated. Patients received 200 mg/day of doxycycline and 600–900 mg/day of rifampicin for 3–21 months, and 1 g/day of streptomycin for 21 days.

Results: The mean age of the 32 patients involved was 21.81 ± 4.09. In total, 10/32 patients did not complete therapy, and the remaining 22 patients received combination antibiotic treatment for a mean of 8.95 ± 4.34 months. Of the 22 patients, 15 underwent MRI, and 7 of them did not consent to MRI. Similarly, 17 patients were followed up by bone scintigraphy, and 5 patients did not have scintigraphy results. In 9/17 patients followed up with bone scintigraphy, sacroiliitis findings were found to reduce after a mean of 7.44 ± 3.71 months, whereas in 12/15 patients on whom MRI was performed, there were no active sacroiliitis findings for a mean of 6.95 ± 2.83 months.

Conclusions: While active involvement findings in bone scintigraphy were observed for a longer period in scintigraphy images, active sacroiliitis findings disappeared in a relatively shorter period of time with MRI. Therefore, we have demonstrated that high-resolution MRI is a very sensitive technique compared to scintigraphy.

Key words: brucellosis; sacroiliitis; imaging techniques; bone scintigraphy; magnetic resonance imaging.

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Introduction

Brucellosis is a zoonosis seen worldwide and is an important cause of morbidity. Although this disease has been controlled via successful public health measures and animal health programs, it remains an important public health problem in developing countries and in Turkey [1-3]. Brucellosis, with unique mechanisms, has the ability to evade the immune system and place itself intracellularly, which results in difficulties in establishing a definite diagnosis; thus, it causes chronic courses in most affected the patients. It is possible to control mortality and morbidity with early diagnosis and treatment. The use of the appropriate antibiotic combinations for an adequate duration is critical in the treatment of brucellosis. One of the most frequent complications of brucellosis is osteoarticular involvement with musculoskeletal symptoms leading to rheumatological manifestations. The most common osteoarticular tables are sacroiliitis, spondylitis, and peripheral arthritis, as well as vertebral osteomyelitis [1,4-6].

In uncomplicated brucellosis cases, successful results can be obtained with six weeks of antibiotic combination therapy. Although there is a consensus that patients with focal involvement require treatment lasting longer than six weeks, exact treatment duration has not been identified. This uncertainty, in addition to quick restoration of normal laboratory values for C-reactive protein (CRP), highlights the fact that improvement in clinical findings and disease serology is not always reliable. Many researchers have recommended that a minimum of three months of combination therapy is required if osteoarticular involvement is detected in brucellosis patients [7]. Imaging modalities, which can be used in the follow-up of patients with bone-joint involvement provide valuable information. Computed tomography (CT) and magnetic resonance imaging (MRI) can be used for this purpose. In this study, we aimed to assess the efficacies of imaging techniques used for determining the cessation of treatment, particularly in young patients with brucellar sacroiliac involvement.

Methodology

This study was conducted in a university hospital serving as a tertiary care referral center in Ankara, Turkey. The study protocol was approved by the institutional review board.

Patient selection and data collection

In this retrospective study, 32 adult patients who had been diagnosed with brucellar sacroiliitis between 2005 and 2010 were included. Data were retrieved from the patients' files. Patients' characteristics, symptoms and findings, and laboratory results such as complete blood count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were recorded in each visit. Additionally, the patients' duration of treatment and treatment regimens were considered.

Brucella IgM, *Brucella* IgG, Rose-Bengal, Wright agglutination test and blood culture results, dedicated sacroiliac joint X-ray, sacroiliac joint MRI, and whole-body bone scan imaging reports were used.

The diagnosis of brucellosis was made by means of positive blood culture or Wright agglutination test at a titer of ≥ 1:160 or by the presence of IgM and IgG antibody against *Brucella* determined by enzyme-linked immunosorbent assay (ELISA). MRI and bone scintigraphy were used to determine involvement of sacroiliac joints.

Dedicated sacroiliac joint X-ray

Sacroiliac joint X-rays were obtained using modified Ferguson images (where the patient lies in supine position with an X-ray tube centered on L5–S1, angled 25–30 degrees in the cranio-caudal direction) for better visualization of the sacroiliac joints. The sacroiliac joints, joint space, irregularity of the joint surfaces, and sclerosis were evaluated.

Whole-body bone scan

The whole-body bone scintigraphy was done using Technetium-99m (Tc-99m) tagged methylene diphosphonate (MDP) (Mon. MDP Kit, Eczacıbaşı, Kocaeli, Turkey). Patients received 15–20 millicurie of Tc-99m MDP. Planar images of the 1-minute perfusion phase, 2 seconds after IV injection and 5 minutes later, and the images of the blood pool for 5 minutes were obtained under a Gamma camera (Millennium, GE, Milwaukee, USA). The whole-bone scan procedure was completed after obtaining images of the whole body, 2–3 hours after injection. The images of the three different phases (*i.e.*, perfusion phase, blood pool phase, and late static phase [bone phase]) were evaluated by a nuclear medicine specialist.

In the evaluation, increased activity in the sacroiliac joint, both in the perfusion phase and the blood pool phase, was assessed. Added to that, diffuse increased dense activity involvement in both sacroiliac joints was considered a positive finding for sacroiliitis.

Sacroiliac joint MRI

The magnetic resonance imaging studies were conducted using 1.5 tesla superconducting machines (Symphony; Siemens, Erlangen, Germany or Philips Gyroscan Intera, Best, The Netherlands). In the sacroiliac joint MRI technique, a 15-minute study, contrast-free images were obtained before intravenous gadolinium injection; if necessary, contrast images were obtained. The images were obtained using high-resolution phase-aligned coils, utilizing the plan and sequences. The activity and chronicity of the disease were considered.

Patients with the following findings were considered to have acute disease. (1) Bone marrow edema: increased intensity in the subchondral region in STIR images; (2) contrast enhancement in the bone marrow: increased intensity due to contrast enhancement in subchondral bone marrow regions in FST1/Gd images; and (3) contrast enhancement in the joint space: increased joint space sections suggesting synovitis indicated by increased contrast enhancement in FST1/Gd images.

Patients with the following findings were considered to have chronic disease. (1) Fatty bone marrow changes: increased area of spaces suppressed in T1-weighted hyperintense with fatty suppression image sequences; (2) erosion: irregularity and patchy areas in joint surfaces in T1 and fat-suppressed sequences; and (3) sclerosis: regions with no signals in all sequences.

Data evaluation

In addition to resolution of symptoms, the following were considered improvement criteria: lack of identification of increased activity in Tc-99m MDP bone scintigraphy, normalization of the laboratory findings, inability to find increased contrast enhancement, and active inflammation findings in sacroiliac MRI images.

For statistical analysis, SPSS version 15.0 (IBM, Armonk, USA) was used. Descriptive statistics using count, percentage, standard deviation, and minimum and maximum values were calculated.

Results

All of the patients were men between 20 and 42 (21.81 ± 4.09) years of age.

Clinical and laboratory results of the patients at initial evaluation

At initial presentation, 21.9% of the patients (7/32) had fever, 46.9% (15/32) had increased ESR, 61.3% (19/31) had elevated CRP, and 15.6% (5/32) had leukocytosis. The Rose-Bengal test was positive in all patients, whereas the Wright agglutination test was positive in 77.8% (21/31), *Brucella* IgM in 45.5% (10/22), and *Brucella* IgG in 91.3% (21/23). Blood culture was done for 10 patients, and *Brucella melitensis* was isolated in 5 of them.

At the begining of treatment, 19/32 patients with a brucellar sacroilitis diagnosis underwent a sacroiliac joint X-ray, while 29 were examined by scintigraphy and 28 by MRI. Only 8/19 (42.1%) patients with sacroiliac joint X-rays had findings consistent with sacroiliitis. Accordingly, 27/29 patients (93.1%) with whole-body bone scans had increased activity in the sacroiliac joints. Of 28 patients undergoing MRI studies, 21 (75.0%) had findings related to sacroiliitis. Of the patients without any findings in sacroiliac joint X-rays, 11 had findings indicating sacroiliitis both in the bone scintigraphy and sacroiliac MRI.

The clinical and laboratory results of the patients at initial evaluation are presented in Table 1.

Clinical and laboratory findings of the patients recorded during follow-up

Fever, increased sedimentation rate, and CRP levels of the patients normalized during the follow-ups. The Wright test, *Brucella* IgM, and *Brucella* IgG turned into

Table 1. The findings of 32 patients with Brucella sacroiliitis diagnosis at initial presentation.

Patient Number	Fever (>38,5 C)	ESR	CRP (>6)	Leukopenia (<4000)	Blood Culture (+)	RB (+)	*Wright* ≥1/160	IgM (+)	IgG (+)	DSI (pathological findings)	Sintigraphy (Increased activity)	MRI (Active Sacroiliitis)
1	-	-	-	-	-	+	+	*	*	-	+	+
2	-	-	-	-	*	+	+	*	*	-	+	*
3	-	+		-	-	+	+	-	+	*	+	+
4	+	+	+	-	+	+	+	+	+	*	+	+
5	-	-	-	-	*	+	-	-	+	*	+	*
6	-	+	+	-	*	+	+	-	+	*	+	+
7	-	+	+	-	*	+	+	-	+	*	+	*
8	-	+	+	-	*	+	-	*	*	*	+	+
9	+	+	+	-	+	+	+	-	+	*	+	*
10	-	-	+	-	*	+	+	-	+	-	+	+
11	-	+	+	-	*	+	+	-	+	*	+	+
12	-	-	-	-	*	+	*	+	+	-	+	+
13	+	+	+	-	+	+	+	+	+	-	+	+
14	+	+	+	+	-	+	*	+	+	+	+	+
15	-	-	-	+	*	+	*	-	+	-	+	-
16	+	-	+	+	-	+	+	-	+	-	+	-
17	-	-	+	-	*	+	*	-	+	*	-	+
18	-	-	+	-	*	*	*	+	-	+	-	+
19	-	-	-	-	*	+	+	*	+	+	+	+
20	-	-	+	+	*	+	-	-	+	-	+	-
21	-	-	-	-	*	+	+	+	+	+	+	-
22	-	+	+	-	*	+	+	-	+	+	+	+
23	-	-	+	-	*	+	+	+	+	+	+	+
24	+	-	-	-	+	+	+	+	-	+	+	-
25	+	+	+	+	+	+	+	+	+	+	+	-
26	-	+	-	-	*	+	+	+	+	*	+	+
27	-	-	-	-	*	+	-	*	*	*	+	+
28	-	-	-	-	*	+	+	*	*	-	+	+
29	-	-	-	-	*	+	-	*	*	*	*	+
30	-	+	+	-	-	+	-	*	*	-	+	-
31	-	+	+	-	*	+	+	*	*	-	*	+
32	-	+	+	-	*	+	+	*	*	*	*	+
Total	**7/32**	**15/32**	**19/31**	**5/32**	**5/10**	**31/31**	**21/27**	**10/22**	**21/23**	**8/19**	**27/29**	**21/28**
%	**21.9**	**46.9**	**61.3**	**15.6**	**50.0**	**100.0**	**77.8**	**45.5**	**91.3**	**42.1**	**93.1**	**75.0**

*This test was not performed on the patient. ESR: erythrocyte sedimentation rate. CRP: C-reactive protein. RB: Rose-bengal test.

negative in a mean of 5.46 ± 2.88, 3.40 ± 2.58, and 6.12 ± 2.65 months, respectively.

Treatment protocol and duration

Twenty-five patients (78.1%) received a triple antibiotherapy regimen consisting of streptomycin (1 g/day intramuscularly for 21 days, rifampicin 1 × 600 mg/day, and doxycycline 2 × 100 mg); the remaining seven were administered a double regimen (21.9%) comprising doxycycline and rifampicin.

Twenty-two patients (68.8%) completed their therapies at a mean of 8.95 ± 4.34 months. These patients' treatments were stopped by the physician after thorough evaluation of their routine clinical, laboratory, and radiological findings. The remaining 10 patients (31.2%) failed to show up for follow-up.

Scintigraphy, MRI findings, and sacroiliac joint x-ray

Twenty-two patients came to regular check-ups, so their treatments were stopped. During the follow-up examinations, no sacroiliac joint X-ray was done on any patient. Serial scintigraphies were performed on 17 of the patients coming for regular follow-ups, but not on the 5 who did not give consent. Similarly, while 15 patients were followed up with MRI findings, 7 did not give consent. At the end of the treatment period, 17 patients had scintigraphic findings and 15 patients had active sacroiliitis shown by MRI. Of the 17 patients followed up with scintigraphy, 9 showed regression at a mean of 7.44 ± 3.71 months, whereas in the remaining patients (47.1%), increased activity persisted for a mean of 9.88 ± 4.26 months. In 12/15 patients (80.0%), active sacroiliitis findings disappeared after a mean of 6.95 ± 2.83 months. However, in the remaining patients, contrast enhancement persisted for a mean of 13.3 ± 2.30 months.

Discussion

Osteoarticular involvement is a frequently seen complication in brucellosis. In various case series, the rate of this occurrence ranges between 10% and 80% [1,5,8]. The most frequently affected area is the lumbosacral region. Sacroiliitis is observed more frequently in younger patients, whereas spondilitis is more frequent in older patients [4,5,9].

Brucella with osteoarticular involvement, such as sacroiliitis and spondylitis, is diagnosed by imaging studies in addition to blood culture and serological tests. Thus, it is unnecessary to conduct joint aspiration or biopsy in these patients [10,11]. For sacroiliitis to be identified with the dedicated sacroiliac joint X-ray, specific radiological changes such as erosion, sclerosis, and fusion must take place in adjacent bony structures. However, radiological changes take place months after the onset of disease symptoms, and since there can be differences interpreting the radiography images, direct X-rays can be misleading in early diagnosis [12,13].

Another imaging modality used to show osteoarticular involvement in brucellosis is bone scintigraphy. Bone scintigraphy is particularly sensitive in the early phases. For the early identification of osteoarticular involvement in brucellosis patients, high-sensitivity Tc-99m MDP whole-body bone scintigraphy is highly recommended [13]. Hoşoğlu *et al.* demonstrated that while only 5/33 (15%) patients had radiological findings consistent with arthritis in X-ray images, 28 (85%) had osteoarticular involvement in their Tc-99m MDP bone scintigraphy tests [14]. In addition, the ability to visualize all body regions without having to administer additional radiopharmaceutical agents makes scintigraphy a more advantageous modality. Scintigraphy gives positive findings in a wide range of situations, including trauma, and is sensitive to metabolic changes in the bone. However, it is reported to have low specificity [9,12-15]. Therefore, it is not a good imaging modality for the differentiation of acute and chronic lesions [15]. MRI is a specific imaging modality, as it allows early diagnosis of osteoarticular involvement and differentiation of acute and chronic lesions, and it helps to visualize soft tissue extensions. It is valuable in differentiating spondylodiscitis from other spinal disorders such as tuberculous spondylitis, pyogenic spondylitis, postoperative changes, spinal degenerative diseases, and vertebral metastasis [10,13,16,17]. In our study, only 8/19 patients (42.1%) evaluated with joint radiography had findings consistent with sacroiliitis. Accordingly, 27/29 patients evaluated with Tc-99m MDP whole-body bone scintigraphy had positive findings, and 21/28 (75%) patients who underwent MRI studies had findings and contrast enhancement indicating active sacroiliitis. Bone scintigraphy and sacroiliac joint MRI findings indicating sacroiliitis were seen in all of the 11 patients who did not have sacroiliitis findings in sacroiliac joint X-ray studies.

In cases of focal involvement, such as osteoarticular involvement, there is no certain laboratory or clinical finding that can be used to make the decision to stop treatment. The most important points are individualizing therapy according to the patient and administering a sufficient duration of antibiotic therapy. Although the optimal duration of therapy in patients with osteoarticular involvement is unknown,

continuation for at least 12 weeks is recommended [7,17-23].

A short time after the initiation of therapy, fever, leukopenia, ESR, and CRP levels return to normal limits. Although improvement in clinical and laboratory findings demonstrates a response, especially in complicated brucellosis patients, it does not provide sufficient information regarding the necessary duration of treatment. In this study, we have shown that body temperature measurements normalized within a week, whereas sedimentation and CRP levels returned normal levels in 14/15 patients (93.3%) within two months. This data is in accordance with a large brucellar spondylodiscitis case series with 294 cases [5].

Serological tests provide very little information in the treatment follow-up. In patients achieving complete cure, IgM and IgG persist in 25% and 90% of the patients, respectively [24]. In our study, in 13/16 patients, the Wright test (81.3%) turned into negative in a mean of 5.46 ± 2.88 months. Similarly, in 5/16 patients, *Brucella* IgM were negative in a mean of 3.40 ± 2.58 months, while in 4/15 patients (26.7%), IgG was found to be negative within 6.12 ± 2.65 months. In the remaining 11 (73.3%) cases, IgG positivity was observed even after the treatment had ended. Although there have been many improvements on diagnostic tests, several challenges remain to be addressed, such as defining specific serological diagnostic and prognostic markers and determining specific and relevant antigenic epitope predictors of each disease stage [25].

MRI is more sensitive than scintigraphy in detecting musculoskeletal infections and more sensitive than CT in disclosing the extent of the disease. This is achieved without the need for intravenous contrast [26]. Aydin *et al*., in a study involving 197 brucellosis patients, showed that patients responded to medical therapy and that MRI findings improved within six weeks to a few months [15]. In our study, the increased activity of 9/17 patients (52.9%) with brucellar sacroiliitis bone scintigraphy findings had disappeared in a mean of 7.44 ± 3.71 months; in the remaining 8 (47.1%), the activity persisted. In 12/15 patients followed up with MRI (80%), no detectable active sacroiliitis findings were present at 6.95 ± 2.83 months; however, in the remaining 3 patients (20.0%), active sacroiliitis findings persisted. In 47% of the patients, the involvement in scintigraphy persisted, which supports the claim that it might persist for a long time [9,12,15,27]. However, since the majority of patients (80%) were followed up with MRI, no active sacroiliitis findings, even before the treatment ended, were observed. This indicates that MRI is more sensitive, and can be used to determine if the treatment can be stopped.

Conclusions

The lack of specific laboratory tests that can be used to decide whether ongoing treatment should be stopped in brucellosis patients with osteoarticular involvement makes imaging techniques more important. Sacroiliac joint X-ray does not provide any significant benefit in patients with sacroiliac joint involvement.

Although bone scintigraphy is a very sensitive technique for detecting osteoarticular involvement, since the increased activity may persist for a long time, it is not suitable for use in follow up [9,12,15,27].

We suggest that in patients with brucellar sacroiliitis, initial evaluation must include a Tc-99m MDP whole-body bone scan; MRI evaluation should be performed in patients with abnormal scintigraphic findings; and MRI can be considered, in addition to clinical and laboratory findings, in determining whether treatment should be stopped, particularly in chronic patients.

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