Evaluation of Bone and Joint Involvement in Patients Followed with the Diagnosis of Brucellosis

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ABSTRACT

Aim: Brucellosis is an important problem all over the world. The most common form is bone-joint involvement. In this study, we planned to reveal our experiences by examining the epidemiological, clinical, laboratory and radiological features of brucellosis cases with and without bone-joint involvement.

Material and Methods: This retrospective clinical study includes the data of 443 patients who were followed up with the diagnosis of brucellosis between December 2014 and August 2019. The epidemiological, clinical, laboratory and radiological findings of the patients were obtained from the patient files and hospital database. Patients were divided into two groups as with and without bone-joint involvement and their data were compared statistically.

Results: A total of 443 patients who were followed up with a diagnosis of brucellosis were included in the study. 92 (20.8%) of these patients had bone-joint involvement of brucellosis (sacroileitis, spondylodiscitis, arthritis, bursitis, synovitis). Magnetic resonance imaging method was used for diagnosis in patients with bone-joint involvement. Patients with bone-joint involvement had longer duration of complaints, and acute phase reactants and agglutination titers were higher.

Conclusion: Bone-joint involvement in brucellosis is very important as it may cause inadequate treatment and may end with sequelae. Radiological imaging is important in the diagnosis of bone-joint involvement, but unnecessary requests should also be avoided. Symptom duration, acute phase reactants, agglutination titer may be guiding for this.

Keywords: Brucellosis; bone-joint involvement; radiological imaging.

Bruselloz tanısıyla Takip Edilen Hastalarda Kemik ve Eklem Tutulumunun Değerlendirilmesi

ÖZ

Amaç: Bruselloz tüm dünyada hala önemli bir halk sağlığı sorunudur. En fazla görülen formu kemik-eklem tutulumudur. Biz bu çalışmada kemik-eklem tutulumu olan ve olmayan bruselloz olgularının epidemiyolojik, klinik, laboratuar ve radyolojik özelliklerini irdeleyip tecrübelerimizi ortaya koymayı planladık.

Gereç ve Yöntemler: Bu retrospektif klinik çalışma, Aralık 2014-Ağustos 2019 tarihleri arasında bruselloz tanısıyla takip edilen toplam 443 hastanın verisini içermektedir. Hastaların epidemiyolojik, klinik, laboratuar ve radyolojik bulguları hasta dosyalarından ve hastane veri tabanından elde edilmiştir. Hastalar kemik-eklem tutulumu olan ve olmayan olarak iki ayrı gruba ayrılıp verileri istatistiksel olarak karşılaştırıldı.

Bulgular: Çalışmaya bruselloz tanısıyla takip edilen toplam 443 hasta dahil edildi. Bu hastaların 92 (%20,8)'si brusellloza ait kemik-eklem (sakroileit, spondilodiskit, artrit, bursit, sinovit) tutulumuna sahipti. Kemik-eklem tutulumu olan hastaların tümünde tanı da manyetik rezonans görüntüleme yöntemi kullanılmıştı. Kemik-eklem tutulumu olan vakalarda şikayet süresi daha uzun, akut faz reaktanları ve aglütinasyon titresi daha yüksekti.

Sonuç: Brusellozda kemik-eklem tutulumu hem tedavi yetersizliğine neden olabileceğinden hem de sekelle sonlanabileceğinden oldukça önemlidir. Kemik ve eklem tutulumunun tanısında radyolojik görüntülemenin önemi büyüktür fakat gereksiz istemlerden de kaçınılmalıdır. Bunun için semptom süresi, akut faz reaktanları, aglütinasyon titresi yol gösterici olabilir.

Anahtar Kelimeler: Bruselloz; kemik eklem tutulumu; radyolojik görüntüleme.

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INTRODUCTION

Brucellosis continues as a public health problem especially in developing countries. Endemic areas are the Mediterranean basin, the Middle East, Central Asia, China, the Indian subcontinent, sub-Saharan Africa and Mexico, and Central and South America (1,2). An estimated 500,000 people are reported to be infected each year in the world, while 2.4 billion are estimated to be at risk from this disease (3). It is reported that the incidence in our country varies between 11.93-49.54 / 100 000 per year (4). The most common routes of transmission are consumption of infected and un pasteurized animal products, mucosal contact with infected animal tissues and secretions, and, to a lesser extent, inhalation of infected aerosols. Brucellosis is also an occupational disease. Shepherds, slaughter workers, veterinarians, dairy industry professionals and laboratory staff are at risk (1).

The sacroiliac joint (80%) and spinal joints (54%) are the most frequently affected areas (7). Peripheral arthritis and sacroileitis are usually seen in the acute period (8). Prosthetic joints can also be affected. Spondylodiscitis is a serious complication of brucellosis. It is more common in elderly patients and patients with long-term illness before treatment. Lumbar vertebrae are more frequently involved than thoracic and cervical vertebrae and may be associated with paravertebral, epidural and psoas abscesses. It is often associated with sequelae (9-11).

In this study, we aimed to investigate the age, sex, underlying diseases, duration of complaints, clinical, laboratory and radiological findings, treatment, treatment duration and sequelae rates of brucellosis patients with and without bone joint involvement.

MATERIAL AND METHODS

Study design and participants

This retrospective clinical study includes the data of 443 patients who were followed up with the diagnosis of brucellosis between December 2014 and August 2019. Patients over 18 years of age who were followed up and treated for brucellosis were included in the study. The aim of the study is to define the epidemiological and clinical characteristics of the patients, laboratory and radiological findings, treatment, treatment durations, and sequelae rates. Then, it is to divide the patients into two groups as patients with and without bone joint involvement and to compare the data statistically.

The data were obtained from patient files and hospital information systems. A control group consisting of patients without bone joint involvement was formed among brucellosis patients who were simultaneously diagnosed and treated in participating centers. Ethics committee approval (Date 28/12/ 2018 and number 188) was obtained for the study.

The diagnosis of brucellosis was made by the standard tube agglutination test (STA) 1/160 and above or by the anti-brucella coombs test with a titer of 1/320 and / or brucella isolation from blood or sterile body fluids.

Exclusion criteria: Patients under 18 years of age and / or those with rheumatologic disease.

Microbiological and serological analysis

Blood samples were inoculated in BacT / ALERT FA plus aerobic bottles (bioMérieux, France) and analyzed in the BacT / ALERT 3D (bioMérieux, France) automated blood culture system. Clinical specimens such as synovial fluid, abscess material, and other body fluids were inoculated on sheep blood agar and chocolate agar. Brucella abortus (strain 99) was used for serological tests.

Radiological analysis

Magnetic resonance imaging (MRI) examinations of cases included in the study during and after active disease were reevaluated retrospectively. 1.5 T MRI (Siemens-Avanto, Siemens Medical System, Germany) was used for imaging. The MRI protocols of the cases were generally determined as T1A and T2A sequences in the axial, coronal and saggital planes, fat suppressed T1A and T2A sequences, contrast enhanced T1A sequences in the axial, coronal and saggital planes, and images of the cases including these sections were included in the study. Gadolinium (0.1 mmol / kg) was used as a contrast agent. Images were evaluated by a radiologist with at least 10 (ten) years of experience.

Treatment

The patients were treated with doxycycline (2x100 mg / day), rifampicin (600-900 mg / day), streptomycin 1 g / day IM, trimethoprim-sulfamethaxazole (160 / 800-320 / 1600 mg / day) orally. Uncomplicated cases were treated for 6-8 weeks and those with bone joint involvement were treated for 6-24 weeks.

Follow

The patients were called for biochemical and serological controls on the 15th, 30th and 45th days of treatment. Patients with bone joint involvement who were treated for a longer period continued to be called once a month.

Data collection

The following data were collected from participating centers and entered into a digital database for each patient:

• Demographic and epidemiological data: Age and gender.

• Clinical, laboratory and radiological data: Time from the onset of complaints to diagnosis, symptoms, serum white blood cell (WBC), erythrocyte sedimentation rate (ESR), C reactive protein (CRP) values, bone joint involvement such as spondylodiscitis, sacroileitis, peripheral arthritis, bursitis regions and radiological findings of this involvement, co-morbid conditions, microbiological and serological findings, treatments given and treatment durations, presence of sequelae.

Statistical Analysis

The patients were divided into two groups as those with bone-joint involvement (Group 1) and those without (Group 2). Statistical analysis was done using SPSS 16.0. Descriptive statistics were presented as frequency and percentage or mean ± standard deviation and appropriate range. Chi-square and Fisher's Exact tests were used to compare categorical variables. Student t-test was used for parametric data and Mann-Whitney U-test was used for non-parametric data in group comparisons, and values from $p < 0.05$ were considered statistically significant.

RESULTS

A total of 443 patients with brucellosis were included in the study. 230 (51.9%) of the patients were male and the mean age was 37.83 ± 16.10 years. 92 (20.8%) of these patients had bone-joint (sacroileitis, spondylodiscitis,

arthritis, bursitis, synovitis) of brucellosis. Of the patients with bone-joint involvement (Group 1), 52 (56.5%) were male and the mean age was 36.75 ± 18.45 years. There was no statistical difference between Group 1 and Group 2 in terms of age (p=0.069) and gender (p=0.321) (Table 1).

Table 1. Comparison of some epidemiological and clinical features of brucellosis cases with bone-joint involvement (Group 1) and without bone-joint involvement (Group 2).

Variable	Total (n=443)	Group 1 (n=92)	Group 2 (n=351)	p value
Male gender, *n* (%)	230 (51.9)	52 (56.5)	178 (50.7)	0.321
Age, SD (*y*)	37,83 ± 16,10	36,75±18,45	38,11±15,55	0.069
Co-morbid diseases,*n* (%)**	111 (25.1)	31 (33.7)	80 (22.8)	**0.015**
Symptoms and signs, *n* (%)				
Fever	157 (35.4)	67 (72.8)	90 (25.6)	**<0.001**
Night sweating	238 (53.7)	57 (62)	181 (51.6)	0.075
Arthralgia	280 (63.2)	64 (69.6)	216 (61.5)	0.155
Weight loss	139 (31.4)	34 (37)	105 (30)	0.201
Back pain	80 (18.1)	42 (45.7)	38 (10.9)	**<0.001**
Weakness	310 (70)	66 (71.7)	244 (69.5)	0.679
Hip pain	44 (9.9)	43 (46.7)	1 (0.3)	**<0.001**

Of the patients, 41 (9.3%) had diabetes mellitus, 27 (6.1%) had hypertension, 20 (4.5%) had heart disease, 11 (2.5%) had chronic obstructive pulmonary disease, 8 (1.8%) had malignancy, 3 (0.7%) had chronic renal failure, 1 (0.2%) had Alzheimer's.

157 (35.4%) of the patients had fever, 280 (63.2%) had arthralgia and 238 (53.7%) had night sweats. All symptoms and signs are shown in Table 1. When the groups were compared, fever, low back pain and hip pain were statistically significant in favor of group 1.

44 (9.9%) patients had sacroiliitis, 40 (9%) had spondylodiscitis, 16 (3.6%) had bursitis, 14 (3.2%) had synovitis, and 10 (2.3%) had arthritis. There were patients with more than one bone joint involvement (Table 2).

Table 2. Sites of involvement in brucellosis patients with bone-joint involvement

Site of involvement	n (%)
Discitis	35 (7.9)
Sacroiliitis	27 (6.1)
Bursitis	5 (1.1)
Bursitis+synovitis	5 (1.1)
Sacroiliitis+arthritis	4 (0.9)
Discitis+sacroiliitis	4 (0.9)
Sacroiliitis+synovitis	4 (0.9)
Arthritis+burcitis+sacroiliitis+synovitis	2 (0.5)
Arthritis+sacroiliitis+synovitis	2 (0.5)
Synovitis	1 (0.2)
Bursitis+discitis+sacroiliitis+synovitis	1 (0.2)
Arthritis+bursitis	1 (0.2)
Arthritis+synovitis	1 (0.2)

Spondylodiscitis involvement was most common in the lumbar region (Table 3).

Table 3. Sites of involvement in brucellar diskitis cases

Site of involvement	n (%)
Lumbar	30 (85.7)
Thoracal	3 (8.6)
Dorsolumbar	1 (2.9)
Cervical	1 (2.9)

Peripheral arthritis involvement sites were 42.8% wrist, 28.6% knee, and 28.6% hip involvement.

When the laboratory values were evaluated, the mean WBC was 10 684 ± 4034, the mean CRP value was 44.5 ± 19.1, the mean ESR was 41.2 ± 14.6, and there was a statistically significant difference between group 2 (p<0.001) (Table 4).

Blood culture was obtained from all patients and 35 (7.9%) of them were positive. There was a difference between the two groups (p<0.001) (Table 4).

Table 4. Comparison of laboratory findings of brucellosis cases with bone-joint involvement (Group 1) and without bone-joint involvement (Group 2)

Variable*	Group 1 (n=92)	Group 2 (n = 162)	p value	Normal
WBC, (x10^9/L)	10.6±4.03	7.05±2.5	<0.001	4-11
CRP, (mg/L)	44.55±19.19	19.74±11.17	<0.001	0-5
ESR, (mm/h)	41.23±14.69	23.6±9.5	<0.001	≤ 20

* Data expressed as Mean ± SD.
Abbreviations: WBC, White blood cell; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate.

Brucella sp grew in 19 (4.3%) patients, *B. melitensis* in 14 (3.2%) and B. abortion in 2 (0.5%) patients. Synovial fluid culture was positive in 7 of 8 patients. In 5 of the synovial fluid culture B. melitensis, 1 of them B. abortus, 1 of them Brucella sp breeding was present.

There was a significant increase in treatment time and complaint duration between groups (p<0.001) (Table 5).

Table 5. Results of microbiological analysis, treatment duration and sequelae data for brucellosis patients with bone-joint involvement (Group 1) and without bone-joint involvement (Group 2)

Variable	Group 1 (n=92)	Group 2 (n=351)	p value
Blood culture	21(22.8)	14(4)	<0.001
Agglutination test ≥ 1:640	45(48.9)	40(11.4)	<0.001
Median treatment duration±SD, *week*	10±3.6	6±0.7	<0.001
Period of complaint±SD, *d*	21±8.5	13±4.6	<0.001
Sequelae, *n* (%)	8 (8.7)	1 (0.3)	<0.001

Sequelae were seen in 9 (2%) patients, but the difference between the groups was significant (p=0.554).

Doxycycline plus streptomycin and doxycycline plus rifampicin plus streptomycin were the most commonly used treatment combinations in the group with bone joint involvement.

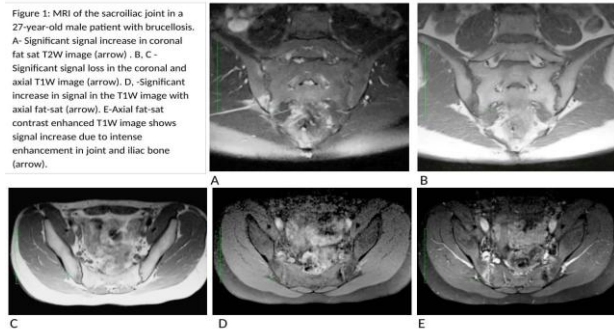## DISCUSSION

Brucellosis is an important public health problem in our country as well as all over the world. It is quite common in the East and South East Anatolia Region, where animal husbandry is widespread in our country (12,13). The population of our study also lives in this region. Brucellosis can affect any organ or system. In addition, since its symptoms and signs may be nonspecific, they

may be overlooked, especially where they are not endemic (14). It most commonly involves the bone-joints. The frequency of bone-joint involvement varies between 10 and 85% in various publications. In our series, this rate is 20.8%. There may be many reasons why the frequency of bone joint involvement is so different. These; virulence of the causative strain, differences in the geographical regions where the studies take place, delays in diagnosis and treatment, and retrospective and limited studies. We know that delayed diagnosis and delayed treatment increase the risk of complications. As a matter of fact, it has been reported that less common bone-joint involvement in patients from the same family may be associated with early diagnosis and early treatment of brucellosis in these individuals (15). Similarly, in our study, the duration of complaints was longer in group 1 patients and there was a delay in diagnosis and treatment.
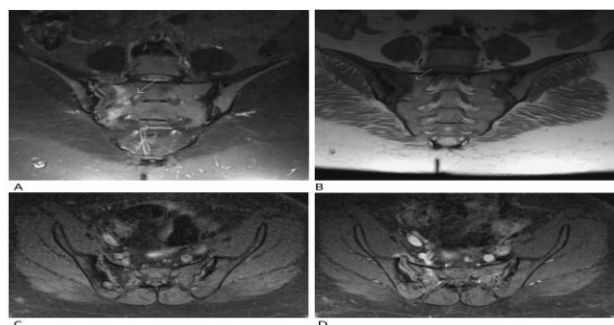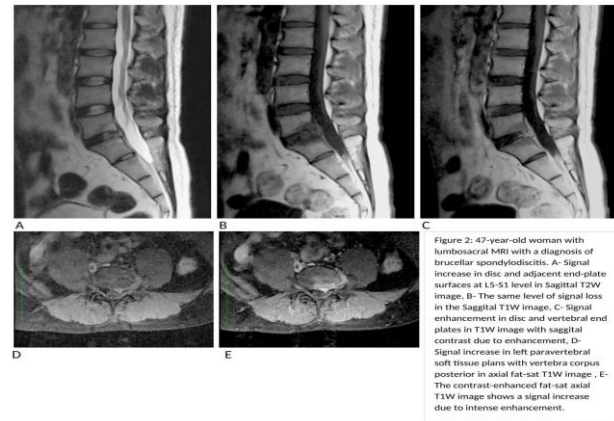
Although bone joint involvement findings are in the form of sacroileitis, arthritis, spondylodiscitis, osteomyelitis and bursitis, respectively, it has been reported that spondiodiscitis is more common in some publications (16,17). In the study of Taşova et al., It was stated that sacroileitis was the most common, and peripheral arthritis most frequently affected the knee joint (18). In another study, Pourbagher et al. stated that sacroileitis was in the front row, and then spondylodiscitis, bursitis, and osteomyelitis were observed, respectively (19). In our series, 44 of 443 patients had sacroiliitis, 40 had spondylodiscitis, then synovitis, bursitis, and peripheral arthritis, respectively. In the study of Bosilkovski et al., It was reported that spondylodiscitis was seen more than sacroileitis (5).Group 1 patients had significantly higher WBC, ESR and CRP levels. In addition, blood culture positivity and agglutination titers were significantly higher in these patients. There are studies reporting that ESR is moderately high in patients with spondylodiscitis (20). In another study, it was reported that agglutination titer increased to 1/640 in two weeks in these patients (21).

Radiological examinations are helpful in determining bone-joint involvement. Direct radiography of the sacroiliac joint may be normal in the early period. Therefore, early bone scintigraphy, computed tomography (CT) and MRI are helpful in the diagnosis (22). The most commonly used method for the detection of spondylodiscitis involvement is MRI. MRI findings of sacroiliitis and spondylodiscitis are generally described as heterogeneous to homogenous contrast enhancement patterns in postcontrast series with signal loss in T1-weighted sequence and increase in signal in T2-weighted sequence in the bony faces and vertebra corpus adjacent to the sacroiliac joint (Figure1,2,3). Other MRI findings; It is sclerosis that presents as late signs of involvement, paravertebral abscess formations and increased contrast with signal changes at the joint level and bursal synovial surfaces, epidural distance and facet joints. Soft tissue involvement is especially important in the presence of abscess and differential diagnosis (23). Brucellar spondylodiscitis most commonly involves the lumbar vertebra (24). Indeed, our series was the same. Distinction of spinal brucellosis from tuberculosis is especially important. It may show radiologically similar

findings in both diseases. Brucella spondylitis most commonly affects the lumbar vertebrae, while tuberculosis affects the thoracic region. Multifocal involvement, skip lesion, paravertebral abscess, collapse of the spine are rare in brucella. Sclerosis in brucellosis is usually focal and localized. The best method to make this distinction is MRI (25). Although radiological examinations are very important for diagnosis, unnecessary radiological examinations should be avoided. As in our series, high acute phase reactants, low back and / or hip pain, high agglutination titer, and prolonged complaint duration may be helpful.

Figure 1: MRI of the sacroiliac joint in a 27-year-old male patient with brucellosis. A- Significant signal increase in coronal fat sat T2W image (arrow) . B, C - Significant signal loss in the coronal and axial T1W image (arrow). D, -Significant increase in signal in the T1W image with axial fat-sat (arrow). E-Axial fat-sat contrast enhanced T1W image shows signal increase due to intense enhancement in joint and iliac bone (arrow).

As for the duration of treatment, there may be treatment failure especially in brucellosis cases with spondylodiscitis with bone-joint involvement. Therefore, longer treatments are preferred. In our patient group, the mean duration of treatment in group 1 patients was 10 weeks and was significantly longer than in group 2. In addition, sequelae rate was again higher in group 2. The limitations of our study are that it is retrospective and the number of patients with bone-joint involvement is not high.

Figure 2: 47-year-old woman with lumbosacral MRI with a diagnosis of brucellar spondylodiscitis. A- Signal increase in disc and adjacent end-plate surfaces at L5-S1 level in Sagittal T2W image, B- The same level of signal loss in the Saggital T1W image, C- Signal enhancement in disc and vertebral end plates in T1W image with saggital contrast due to enhancement, D- Signal increase in left paravertebral soft tissue plans with vertebra corpus posterior in axial fat-sat T1W image , E- The contrast-enhanced fat-sat axial T1W image shows a signal increase due to intense enhancement.

Figure 3: Sacroiliac Joint MRI of a 24-year-old male patient with brucellar sacroileitis. A- Marked signal increase in the right sacral vertebral wing in the fat-sat coronal T2W image (arrow), B-Significant signal loss in the same region in the coronal T1W image (arrow), C- The axial fat-sat T1W image with shows a low signal on the right sacral vertebral wing adjacent to the joint. D- In the axial fat-sat contrast enhanced T1W image the signal increase due to the same level of intensive and heterogeneous enhancement was observed.

CONCLUSION

As a result, it is important not to overlook the diagnosis, especially in regions where brucellosis is endemic, in early treatment. It is clear that early diagnosis and treatment will also minimize bone joint complications, which are more difficult to treat and have a higher rate of sequelae. In addition, fever, low back / hip pain and high laboratory values may be a guide especially in the use of radiological methods such as MRI in determining the bone joint involvement and in determining the correct indications to avoid unnecessary requests. However, it is obvious that prospective studies with more patients are needed for this.

No conflict of interest

Authors's Contributions: Idea/Concept: S.K.; Design: S.K.; Data Collection and/or Processing: S.K.; Analysis and/or Interpretation: S.K., S.K.; Literature Review: S.K., S.K.; Writing the Article: S.K.; Critical Review: S.K.

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