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Original Article

Spondylodiscitis: a common complication of brucellosis

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Abstract

Introduction: Brucellar spondylodiscitis is a frequent and serious complication of brucellosis. The aim of this study is to describe the brucellosis patients with spondylodiscitis and the predictive factors related to spondylodiscitis in brucellosis.

Methodology: Laboratory-confirmed brucellosis patients from a low- to medium-endemic region were enrolled in the study and distributed into two groups. Group I consisted of patients with spondylodiscitis and Group II patients had no complications. Both groups were compared for predictive factors of spondylodiscitis.

Results: A total of 219 patients with active brucellosis were included in the study. We determined at least one complication in 91 (41.6%) patients. The most frequent complication was spondylodiscitis [n = 59 patients (26.9 %)]. In univariate analysis, age, time from symptom onset to diagnosis, presence of low back pain, increased levels of erythrocyte sedimentation rate, and alkaline phosphatases were the most significant predictive factors for spondylodiscitis among brucellosis cases. Presence of headache and thrombocytopenia were less frequent in patients with spondylodiscitis when compared to patients without complications ($p = 0.024$, $p = 0.006$ respectively). In multivariate analysis, old age (odds ratio [OR] 1,063; 95% confidence interval [CI] 1.026-1.101; $p < 0.001$), prolonged time between symptoms onset before diagnosis (OR 1.008; 95% CI 1.001-1.016; $p = 0.031$), and presence of low back pain (OR 12.886; 95% CI 3.978-41.739; $p < 0.001$) were indepedently associated with an increased risk of spondylodiscitis.

Conclusions: Spondylodiscitis is the most frequent complication of systemic brucellosis. Patients with low back pain, older age, and longer duration of symptoms should be considered as candidates of potential spondylodiscitis in brucellosis.

Key words: Brucellar spondylodiscitis; clinical; diagnosis; epidemiology.

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Introduction

Brucellosis remains one of the most common zoonotic diseases worldwide, although it occurs mainly in the Mediterranean area, the Middle East, parts of Central and South America, and possibly sub-Saharan Africa [1]. In Turkey, brucellosis is an important public health problem, and it is still an endemic disease. Limited veterinary support services and husbandry practices favor the spread of infection [2]. Moreover, in recent years there has also been uncontrolled migration from surrounding countries such as Syria, Iran, Iraq where brucellosis is endemic [2-4]. More than 3.5 million Syrian refugees immigrated to Turkey in the last 7 years and this also brought about a huge amount of uncontrolled movement and smuggling of animals across borders. Uncontrolled animal movements can contribute to the spread and persistence of zoonotic diseases in a regional context [2-5].

According to reports of the Turkish Ministry of Health, the incidence rate of brucellosis cases was 5.30-16.73/100 000, annually, between 2006 and 2016 [6]. Although brucellosis is an infection with minimal mortality, it can lead to several organ-based complications, such as osteoarticular involvement, endocarditis, neurobrucellosis, epididymoorchitis, and liver involvement [7]. Osteoarticular complications such as peripheral arthritis, spondylodiscitis, sacroiliitis, osteomyelitis, tenosynovitis, and bursitis are the most common complications [8]. Among osteoarticular complications, spondylodiscitis is a frequent and serious complication of brucellosis. Antibiotic treatment is mostly successful in early stages with no or minor neurological deficits; however, diagnosis may be delayed, due to the insidious onset of symptoms, development of abscess formation in the adjacent tissues, and disabiling neurological deficits [9-11]. Thus, early diagnosis is important. In this study, the aim was to describe the clinical features and laboratory findings among brucellosis patients with

spondylodiscitis, and to determine predictive factors for the development of spondylodiscitis in brucellosis.

Methodology

This prospective, observational study was conducted between January 2007 and December 2016 in Pamukkale University Hospital in Denizli, Turkey, a tertiary-care teaching hospital that provides health care service for approximately 1-1.2 million people. During the study period, demographic data, medical history (including epidemiologic risk factors and transmission routes), physical examination, laboratory results, complications, and treatment were recorded on individual, structured patient forms. The diagnosis of brucellosis was made according to clinical features and laboratory evidence that include: positive Brucella Wright agglutination test with ≥ 1/160 titers, positive Brucella Coombs test with a titer of ≥ 1/320, and/or the isolation of the *Brucella* species from blood or other body fluids or tissue samples [12].

The patient's clinical presentation was categorized into one of three phases based on the duration of patients's symptoms: acute (0–2 months), subacute (2–12 months), and chronic (> 12 months) [13].

In the case brucella symptoms reappearing, a relapse was considered by a positive blood culture test or by increased titers of previous serological tests after cessation of the treatment.

In the case of infection symptoms or physical signs at a particular anatomic site, complications were diagnosed by performing the following: radiologic examinations, such as plain X-ray, ultrasound (USG), computerized tomography (CT), magnetic resonance imaging (MRI), echocardiography, and microbiological tests such as isolation of *Brucella* spp. from body fluids. Diagnosis of spondylodiscitis was made according to the clinical findings and characteristic changes on MRI or CT scans [14].

The patients were grouped into Group I if they had spondylodiscitis and Group II if they had no complications. In order to determine the predictive factors for spondylodiscitis among brucellosis cases, we compared factors such as age, time from symptom onset to diagnosis, number of relapses, accompanying diseases, clinical symptoms, and physical and laboratory findings between groups.

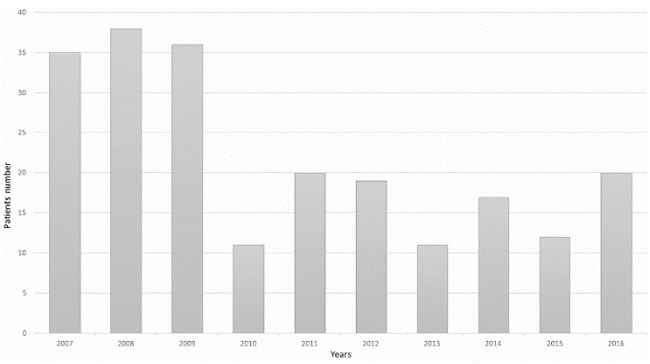
Statistical analysis was performed by SPSS for Windows 23.0 (SPSS, Chicago, IL, USA). Mean and standard deviations are given in cases of normal distribution; otherwise, the data was presented as median (range). Student *t*-test was used for parametric data; the Mann-Whitney U-test was used for nonparametric data for group comparisons; and Pearson chi-square or Fisher exact tests were used for categorical data analysis. Differences were considered statistically significant when the p value was < 0.05. Backward stepwise multiple logistic regression was performed to identify the independent predictive factors associated with an increased risk of spondylodiscitis.

Results

A total of 219 patients with active brucellosis were included in the study, and their annual distribution during the study period is shown in Figure 1. There was a remarkable number of brucellosis cases between 2007 and 2009. During the following years between 2010 and 2016 there was a stable trend of cases. Of the patients, 113 (51.6%) were male; the mean age was 48.5 ±15.9 (range: 16–78) years. Of the cases, 110 (50.2%) were dealing with livestock, and 36 (30.3%) of them had an abortus history of their animals. 137 (62.6%) patients had a history of consuming raw or unpasteurized milk and other dairy products, and 3 (1.4%) had laboratory contact. In 25 patients (11.4%), brucellosis was recently reported in family members. In 158 (72.1%) cases, the disease course was acute; in 47 (21.5%) cases, subacute; and in 14 (6.4%), chronic. Twenty four (11%) of the patients were considered to have relapsed. The most common presenting symptoms were weakness (73.1%), low back pain (58.9%), fever (68.4%), and night sweating (57.1%) (Table 1). Of the 120 patients from whom blood samples for culture were obtained at admission, *Brucella* spp. was isolated from the blood cultures in 59 (49.2%) patients. Typing was possible for only 17 isolates, yielding 14 for *Brucella melitensis* and 3 for *Brucella suis.*

Of the 219 patients, 91 (41.6%) had complications, while 128 patients were without complications. The most frequent complication was spondylodiscitis, which was present in 59 (26.9%) patients (Table 1). Lumbar involvement was seen in 41/59 (69.5%)

Figure 1. Annual distribution of brucellosis from 2007 to 2016.



patients; the L3-L4 segment was the most frequently involved level, with a rate of 15/59 (25.4%) patients. More than one level was affected in 15/59 (25.4%) patients. In 25 (42.4%) spondylodiscitis patients, abscess was present, and paravertebral involvement was the most frequent site (28.8%) (Table 2). Slight paraparesis developed in only one patient. Forty-one (69.5%) patients with spondylodiscitis were treated with triple combination therapy, and the others received dual combination therapy. In triple combinations, 25 (42.4%) patients received rifampicin, doxycycline, and trimethoprim sulfamethoxazole, while 16 (27.1%) received rifampicin, doxycycline, and aminoglycoside (streptomycin or gentamicin). In dual combinations, 17 (28.8%) patients received rifampicin plus doxycycline, the remaining one (1.7%) patient received doxycycline plus streptomycin. Median duration of antibiotic therapy was 6 (range: 4-9) months. In seven patients, abscess drainage was necessary; in another, total laminectomy and posterior instrumentation were required.

Old age, prolonged time between symptom onset and diagnosis, presence of low back pain, increased erythrocyte sedimentation rate (ESR), and alkaline phosphatase (ALP) were significant predictive factors of spondylodiscitis among brucellosis cases in univariate analysis ($p < 0.05$). Presence of headache and thrombocytopenia were less frequent in patients with spondylodiscitis when compared to patients without complications ($p = 0.024$ and $p = 0.006$, respectively) (Table 3).

In multivariate analysis, old age (odds ratio [OR] 1.063; 95% confidence interval [CI] 1.026-1.101; $p < 0.001$), prolonged time between symptom onset and diagnosis (OR 1.008; 95% CI 1.001-1.016; $p = 0.031$), and presence of low back pain (OR 12.886; 95% CI 3.978-41.739; $p < 0.001$) were indepedently associated with an increased risk of spondylodiscitis (Table 4).

Discussion

Brucellosis remains a public health problem worldwide, as well as in Turkey. The incidence of the disease is variable in different regions of the country. Denizli, where the study was conducted, is a low- to medium-endemic area; during the first three years (2007-2009) of the study, patient enrollment was higher. This difference of enrollment between the first three years and the following seven years parallels the annual incidence rates reported by the Turkish Ministry of Health for *Brucella* cases [6,15].

Table 1. Symptoms, signs, laboratory findings and complications of patients with brucellosis.

Features	Patients, n (%)
Symptoms	
Fever	129 (58.9)
Chills	104 (47.5)
Night sweating	125 (57.1)
Weakness	160 (73.1)
Anorexia	86 (39.3)
Arthralgia	108 (49.3)
Low back pain	129 (58.9)
Upper back pain	38 (17.4)
Headache	49 (22.4)
Hip pain	46 (21)
Abdominal pain	26 (11.9)
Weight loss	38 (17.4)
Nausea / vomiting	28 (12.8)
Scrotal pain, swelling *	6 (5.3)
Physical findings	
Body temperature ≥ 37.5°C	89 (40.6)
Hepatomegaly	16 (7.3)
Splenomegaly	15 (6.8)
Lymphadenopathy	4 (1.8)
Epididymo-orchitis *	6 (5.3)
Rash	3 (1.4)
Laboratory findings	
Leukopenia (Leukocyte count < 4000/mm^3)	11 (5)
Leukocytosis (Leukocyte count > 11000/mm^3)	11 (5)
Anemia (female ≤ 12 g/dL and male ≤ 13.5 g/dL)	118 (53.9)
Thrombocytopenia (Platelet < 150 000/mm^3)	18 (8.2)
Thrombocytosis (Platelet > 450 000/mm^3)	15 (6.8)
Elevated alanine transaminase > 40 U/L	47 (21.5)
Blood culture positivity, 120 patients	59 (49.2)
Complications	
Spondylodiscitis	59 (26.9)
Peripheral arthritis	11 (5)
Knee	8
Hip	2
Elbow	1
Sacroiliitis	9 (4.1)
Neurobrucellosis	12 (5.5)
Urogenital system	8 (7.1)
Epididymo-orchitis	6
Prostatitis	2
Cutaneous	3 (1.4)
Bursitis	2 (0.9)
Endocarditis	1 (0.5)
Lung involvement	1 (0.5)

*: Percentage calculated based on number of male patients.

Table 2. Characteristics of spondylodiscitis among 59 patients.

Vertebral involvement	Patients, n (%)
Lumbar	27 (45.8)
Thoracic	12 (20.3)
Thoracolumbar	9 (15.2)
Cervical	5 (8.5)
Sacral	1 (1.7)
Lumbosacral	5 (8.5)
Localization of abscess	25 (42.4)
Paravertebral	14 (23.7)
Epidural	7 (11.9)
Psoas	1 (1.7)
Epidural + paravertebral	2 (3.4)
Paravertebral + psoas	1 (1.7)
Multiple (> 2 vertebrae) involvement	15 (25.4)
Procedure	7 (11.9)
Abscess drainage	5 (8.5)
Abscess drainage and laminectomy	1 (1.7)
Abscess drainage and posterior instrumentation	1 (1.7)

In our study, *Brucella* spp. was isolated in nearly half of the blood cultures, although species typing was possible for only 17 isolates (yielding 14 for *Brucella melitensis* and 3 for *Brucella suis*). Since pig farming is not common in Turkey, no cases of *B. suis* were seen until the first human infection that we recently reported [16]. The patient who had neurobrucellosis is also one of the cases of this study. Of the remaining two cases, one had spondylodiscitis (T10-11 segment involvement), and the other one had no complications.

As mentioned above (see Introduction), brucellosis can cause significant complications [7]. In the present study, of the 219 patients with brucellosis, complications were present in 91 (41.6%) patients; the most frequent complication was spondylodiscitis, present in 59 (26.9%) patients. In previous reports, the spondylodiscitis rate in brucellosis was 11.9-39% [17-20]. Aktug-Demir N *et al.* [21] reported a spondylodiscitis rate of 23.7%, which is similar to our data. However, different from our results, in another study from Turkey reported a very low spondylodiscitis rate as 5.6% [22].

Distribution of osteoarticular involvements can be very diverse, and some studies reported sacroiliitis as the most common complication [23-25], whereas others reported spondylodiscitis as the most common [18,26]. In our study, we found that the frequency of sacroiliitis was very low (4.1%). The differences in distribution of osteoarticular complications among studies may be due to age differences among study groups. Sacroiliitis is frequent in younger patients, while spondylodiscitis is more common in older patients, such as those in our study group [27]. In addition, our hospital is a regional reference center that serves more complicated patients, and this may be another possible reason for the high prevalence of spondylodiscitis.

In brucellosis, the spinal column can be affected at any level, whereas lumbar spine is the most common site, particularly the L4-L5 segment [28]. Our results showed that lumbar involvement was the most frequent site (69.5%) for spondylodiscitis, and one-quarter of spondylodiscitis cases involved the L3-L4 segment. In previous studies, lumbar involvement was reported as 60-78% in patients with brucellar spondylodiscitis [20,29,30]. One of these studies, the most common site was the L4–L5 segment; the level was not specified in the two other studies.

In our series, abscess formation in and around the infected area was also frequent (42.4%); the paravertebral site was especially common (28.8% of cases with spondylodiscitis). Similarly, a recent study reported an abscess formation rate of 39.5% and paravertebral involvement rate of 21.4% [31]. In another study, abscess formation and paravertebral involvement were very high, at rates of 81% and 58.3%, respectively [29]. Kouba M *et al.* [20] found an even higher rate of paravertebral abscess at 65.6% of brucellar spondylodiscitis cases. Kaptan F *et al.* [19] reported that abscess was found in 61.3% of patients with brucellar spondylodiscitis and emphasized the higher sensitivity of MRI to detect abscess.

Although some studies revealed that sex might be important in spondylodiscitis, our results showed that it was not a significant factor [19,21].

Table 3. Univariate analysis for the predictive factors of spondylodiscitis among brucellosis cases.

Variable	Group 1 Spondylodiscitis N = 59 (%)	Group II No complications N = 128 (%)	P value
Age, year, median (IQR)	57 (48-70)	45 (32.25-56)	< 0.001
Male sex, n = 92 (%)	26 (44.1)	66 (51.6)	0.341
Median (IQR) time symptoms onset to diagnosis, day	45 (30-90)	30 (15-47.5)	< 0.001
Relapse, n = 24 (%)	8 (13.6)	13 (10.2)	0.493
Accompanying diseases			
Diabetes mellitus	7 (11.9)	9 (7.1)	0.279
Renal insufficiency	2 (1.6)	0	1
Connective tissue diseases	1 (1.7)	5 (4)	0.411
Coroner artery diseases	2 (3.4)	4 (3.1)	1
COLD	3 (5.2)	4 (3.1)	0.680
Symptoms			
Fever	32 (54.2)	73 (57.0)	0.720
Chills	28 (47.5)	59 (46.1)	0.862
Weakness	45 (76.3)	92 (71.9)	0.528
Arthralgia	35 (59.3)	58 (45.3)	0.075
Night sweating	35 (59.3)	73 (57)	0.768
Anorexia	28 (47.5)	42 (32.8)	0.054
Low back pain	52 (88.1)	59 (46.1)	< 0.001
Upper back pain	15 (25.4)	19 (15.2)	0.095
Headache	6 (10.2)	31 (24.4)	0.024
Hip pain	12 (20.3)	25 (19.5)	0.897
Abdominal pain	7 (11.9)	14 (10.9)	0.852
Nausea / vomiting	7 (11.9)	14 (10.9)	0.852
Weight loss	9 (15.3)	20 (15.9)	0.914
Physical examination			
Body temperature ≥ 37.5°C	20 (33.9)	49 (38.3)	0.564
Lymphadenopathy	0 (0)	4 (3.1)	0.310
Hepatomegaly	5 (8.5)	6 (4.7)	0.313
Splenomegaly	2 (3.4)	10 (7.8)	0.345
Laboratory findings			
Leukopenia (leukocyte count < 4000/mm^3)	1 (1.7)	9 (7)	0.174
Leukocytosis (leukocyte count > 11000/mm^3)	4 (6.8)	5 (3.9)	0.567
Anemia (female ≤ 12 g/dL and male ≤ 13.5 g/dL)	32 (54.2)	69 (53.9)	0.966
Thrombocytopenia (platelet < 150 000/mm^3)	0 (0)	14 (10.9)	0.006
Thrombocytosis (platelet > 450 000/mm^3)	6 (10.2)	8 (6.3)	0.344
Elevated alanine transaminase > 40 U/L	10 (16.9)	31 (24.2)	0.264
Blood culture positivity, 93 patients	13 (40.6)	34 (55.7)	0.166
C-reactive protein, mg/dL	3.88 (4.07)	3.18 (4.51)	0.307
Sedimentation, median (IQR)	46 (27-79)	29 (16-50)	< 0.001
Alkaline phosphatases, IU/L, median (IQR)	110 (84-140)	91 (68.25-116)	0.003
Therapy duration, months, mean (SD)	6 (4-9)	1.5 (1.5-2)	< 0.001

IQR: Interquartile Range.

Table 4. Multivariate analysis for the predictive factors of spondylodiscitis among brucellosis cases.

Predictive factors	OR	95% CI	P value
Age, year, median (IQR)	1.064	1.028-1.102	< 0.001
Median (IQR) time symptoms onset to diagnosis, day	1.008	1.001-1.016	0.031
Low back pain	12.886	3.978-41.739	< 0.001

IQR: Interquartile Range; OR: Odd Ratio; CI: Confidence Interval.

The presence of low back pain, older age, and prolonged time between symptom onset and diagnosis were significant independent predictive factors for spondylodiscitis development in our series. Our results revealed that there is an approximately 13-fold increased risk of spondylodiscitis in brucellosis cases with low back pain. Similarly, previous studies showed that 'back or neck pain' was the most frequent symptom [20,32].

Older age is another important predictive factor of spondylodiscitis in brucellosis patients, and our results revealed that patients with spondylodiscitis were more likely to be older, with median age as 57 [13,32]. Similarly, previous studies reported that [21,33] spondylodiscitis was most frequent in older patients.

The prolonged time between the onset of symptoms and the appearance of radiological changes may prevent early diagnosis, thus increasing the risk for spondylodiscitis [20]. In our study, even a minor delay (45 days vs. 30 days) in diagnosis was an important predictive factor of spondylodiscitis in brucellosis patients. Although previous studies reported longer delays in diagnosis, even minor delays can be significant in the development of complications [13,20,28,32]. Therefore, in older patients and in patients who have back pain, earlier diagnosis and treatment of brucellosis may prevent complications like spondylodiscitis.

Our results showed that ESR and ALP were significant predictive factors of spondylodiscitis among brucellosis cases in the univariate analysis, which may be related to bone infection. Additionally, our multivariate analysis did not prove that these parameters are independent predictive factors. Aktug-Demir N *et al.* [21] reported that ESR was independently associated with brucellar spondylodiscitis. Bosilkovski *et al.* [33] showed that significantly-higher ESR was associated with osteoarticular brucellosis in univariate analysis. Another study found that a total of 78.6% of patients with infective spondylodiscitis had elevated ESR, and 55.6% had elevated levels of ALP [11].

Headache and thrombocytopenia were more frequent in patients without complications in the univariate analysis ($p = 0.024$, $p = 0.006$, respectively). As acute symptoms and discovery of infection, frequent complaint of headache and thrombocytopenia can be expected in patients without complications.

The optimal duration of spondylodiscitis treatment is not clear; however at least 3-6 months of treatment is recommended [13,20]. Mean treatment duration was six months among our patients. In 25 (42.4%) patients whose spondylodiscitis was complicated with either epidural, paravertebral, or psoas abscess, surgical drainage was performed as necessary.

We could not perform blood sampling and *Brucella* species typing with all of our patients, which is a limitation of this study. As a result, we could not determine the relationship between *Brucella* species and spondylodiscitis development.

Conclusion

Even though the incidence of brucellosis is decreasing with time, serious complications that impact treatment and morbidity are still challenging. Spondylodiscitis is the most frequent complication of systemic brucellosis, especially in older patients. In patients with a significant delay between symptom onset and diagnosis, the presence of complications should be kept in mind at the time of diagnosis. Low back pain and older age are the most significant predictive factors of spondylodiscitis. Earlier consideration of spondylodiscitis in this patient population may prevent treatment delays and morbidity.

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