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Research Article

Evaluation of clinical features and follow-up results of brucella spondylodiscitis cases

Brusella spondilodiskiti olgularının klinik özellikleri ve izlem sonuçlarının değerlendirilmesi

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Abstract

Introduction: Since there is no standard treatment regimen and duration in brucellosis spondylodiscitis cases, management of brucellosis spondylodiscitis cases is difficult. This study aimed to evaluate the risk factors, clinical features and follow-up results of brucellosis spondylodiscitis cases followed up in a tertiary healthcare institution.

Methods: In this retrospective study, data from 60 patients with brucellosis spondylodiscitis who were followed up in a training and research hospital between 2009-2019 were evaluated from the electronic data recording system. All statistical analyses were performed using the SPSS 26 program. Comparison of the distributions of variables in the compared groups was made using the chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables.

Results: A total of 212 patients were followed up with a diagnosis of brucellosis. Spondylodiscitis was detected in 60 (28.30%) cases. In cases developing brucella spondylodiscitis, the duration of symptoms was longer (p=0.007), lower back pain (p=0.000), muscle pain (p=0.023) were more common and sedimentation values were higher (p=0.044). Three (5%) cases had single vertebra involvement, 34 (56.70%) cases had two vertebra involvement and 23 (38.30%) cases had ≥3 vertebra involvement. The most common involvement was in the lumbar region (23 cases, 38.30%), followed by the thoracic region (13 cases, 21.70%) and lumbosacral region (11 cases, 18.33%). Abscess was detected in 21 (35%) cases. Seventeen (28.30%) cases were given a treatment regimen containing two antibiotics and 43 (71.70%) cases were given a treatment regimen containing three antibiotics. Treatment regimens containing three antibiotics were found to be more successful (p=0.001). The mean treatment duration of the cases was 19.7±12 weeks (minimum 12-maximum 66 weeks). Relapse occurred in five (8.30%) cases. While muscle weakness and neurological deficits developed in three (5%) cases, two of them underwent surgery.

Conclusion: Brucella spondylodiscitis is a not uncommon manifestation of the disease. In most cases, more than one vertebral involvement was affected. Treatment regimens containing three antibiotics were found to be more successful than regimens containing two antibiotics. Cases with muscle weakness and neurological deficits as complications were detected. A team consisting of infectious diseases, radiologists, neurosurgeons and physical therapy specialists may be useful for the treatment of spondylodiscitis.

Keywords: Brucellosis, spondylodiscitis, complication

Öz

Giriş: Brusella spondilodiskiti olgularında standart bir tedavi rejimi ve süresi olmadığı için brusella spondilodiskiti olgularının yönetimi zordur. Bu çalışmada üçüncü basamak bir sağlık kuruluşunda izlenmiş olan bruselloz spondilodiskiti olgularının risk faktörleri, klinik özellikleri ve izlem sonuçlarının değerlendirilmesi amaçlanmıştır.

Yöntem: Retrospektif olarak planlanan bu çalışmada bir Eğitim ve araştırma hastanesinde 2009-2019 yılları arasında takip edilen 60 brusella spondilodiskiti tanılı hastaya ait veriler elektronik veri kayıt sisteminden değerlendirilmiştir. Tüm istatistiksel analizler SPSS 26 programı kullanılarak yapılmıştır. Karşılaştırılan Gruplardaki değişkenlerin dağılımlarının karşılaştırılması kategorik değişkenler için ki kare testi veya Fisher's exact testi, sürekli değişkenler için ise Mann-Whitney U testi ile yapılmıştır.

Bulgular: Bruselloz tanısıyla toplam 212 hasta takip edilmiştir. Altmış (%28,30) olguda spondilodiskit tespit edilmiştir. Brusella spondilodiskit gelişen olgularda semptom süresi daha uzun (p=0,007), bel ağrısı (p=0,000), kas ağrısı (p=0,023) daha sık ve sedimentasyon değerleri daha yüksekti (p=0,044). Üç (%5) olguda tek vertebra tutulumu, 34 (%56,70) olguda iki vertebra tutulumu ve 23 (%38,30) olguda ≥3 vertebra tutulumu vardı. En sık tutulum lomber bölgede (23 olgu, %38,30) görülürken bunu torasik bölge (13 olgu, %21,70) ve lumbosakral bölge (11 olgu, %18,33) takip etmiştir. Yirmi bir (%35) olguda apse saptanmıştır. On yedi (%28,30) olguya iki antibiyotik kombinasyon rejimi ve 43 (%71,70) olguya üç antibiyotik kombinasyon rejimi verilmiştir. Üç antibiyotik kombinasyon rejiminin daha başarılı olduğu bulunmuştur (p=0,001). Olguların ortalama tedavi süresi 19,7±12 haftaydı (minimum 12-maksimum 66 hafta). Beş (%8,30) olguda relaps meydana gelmiştir. Üç (%5) olguda kas güçsüzlüğü ve nörolojik defisitler gelişirken, ikisi ameliyata alınmıştır.

Sonuç: Brucella spondilodiskit hastalığın nadir olmayan bir belirtisidir. Çoğu olguda birden fazla vertebral tutulum etkilenmiştir. Üç antibiyotik kombinasyon rejiminin iki antibiyotik içeren rejimlerden daha başarılı olduğu bulunmuştur. Komplikasyon olarak kas güçsüzlüğü ve nörolojik defisitler olan olgular saptanmıştır. Spondilodiskit tedavisinde enfeksiyon hastalıkları, radyologlar, beyin cerrahları ve fizik tedavi uzmanlarından oluşan bir ekibin yardımı faydalı olabilir.

Anahtar Sözcükler: Bruselloz, spondilodiskit, komplikasyon

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Key Points

1. Brucella spondylodiscitis is a rare and difficult complication to manage.
2. A multidisciplinary approach consisting of infectious diseases, radiologists, neurosurgeons and physical therapists is required for the management of brucellosis cases.

Introduction

Brucellosis is the most common microbial zoonotic disease in the world and is endemic in most developed and developing countries. Brucella, an intracellular bacterium, causes brucellosis and Brucella melitensis spp. is the most common Brucella species [1]. Thousands of new brucellosis cases are reported worldwide each year: The annual incidence per million population is 238.6 in Iran, 262.2 in Türkiye, 214.4 in Saudi Arabia and 278.4 in Iraq [2]. Humans can acquire the infection mainly through occupational contact (e.g. veterinary, butchery, animal husbandry) or through consumption of contaminated dairy products, especially milk, butter, and cheese [1,2]. Brucellosis can affect the human body systemically. The most common clinical presentations of human brucellosis are fever, sweating, musculoskeletal pain, lymphadenopathy, or hepatosplenomegaly. It can affect almost any organ and system, especially the musculoskeletal system. Arthritis, bursitis, tenosynovitis, sacroiliitis, spondylodiscitis, and osteoeomyelitis can be observed in musculoskeletal system involvement [1,2]. Since there is no standard treatment regimen and duration in brucellosis-related spondylodiscitis cases, management of brucellosis-two related spondylodiscitis cases is difficult. This study evaluated the risk factors, clinical features, and follow-up results of brucellosis-related spondylodiscitis cases followed in a tertiary healthcare institution.

Methods

In this retrospective study, data belonging to 60 patients diagnosed with brucella spondylodiscitis who were followed up in a training and research hospital between 2009-2019 were evaluated from the electronic data recording system. Data related to the patients' demographic, clinical characteristics, laboratory findings, antibiotic treatments received, treatment responses and surgical treatment requirements were recorded.

Ethical approval, informed consent and permissions

Ethical approval for this study was obtained from the Health Sciences University Izmir Bozyaka Training and Research Hospital Health Research Ethics Committee (No: 5, Date: 12/06/2009). Since the study was retrospective, informed consent could not be obtained.

Study design

Brucella spondylodiscitis was diagnosed according to the criteria of having a clinical picture compatible with spondylodiscitis, radiological demonstration of inflammation of one or more vertebrae and/or intervertebral discs and microbiological confirmation of the diagnosis of brucellosis. Microbiological criteria are isolation of bacteria from blood, body fluid and tissue samples, positive standard Wright agglutination test or growth in culture. Serological diagnostic criteria are positivity of 1/160 and above or ≥4-fold increase in antibody titer at 14-day intervals. Patients are classified as acute (<2 months), subacute (2 months-12 months) and chronic (>12 months) according to the duration of symptoms [1-3].

Treatment failure is the persistence of clinical signs and symptoms at the end of the three-month treatment period. Relapses is the reappearance of clinical signs and symptoms during the follow-up period, a decrease in tube agglutination titer followed by an increase again or the isolation of *Brucella spp*. in the blood culture. Pain, abnormal physical examination findings or limitation of movement 6 months after treatment are defined as sequelae.

Statistical analysis

All statistical analyses were performed using SPSS 26 program (Statistical Product and Service Solutions for Windows, version 26.0, IBM Corp., Armonk, NY, USA). In comparing the distributions of variables in the groups, the chi-square test or Fisher exact test was used for categorical variables, and the Mann-Whitney U test was used for continuous variables. $p<0.05$ was considered significant.

Results

A total of 212 patients were followed up with the diagnosis of brucellosis. The age range of the patients was 16-81 years, with a mean of 48.60±15.30 years. Spondylodiscitis was detected in 60 (28.30%) cases. The comparison of cases with and without brucellosis spondylodiscitis in terms of demographic characteristics, clinical and laboratory findings is shown in Table 1.

In cases with Brucella spondylodiscitis, the duration of symptoms was longer ($p=0.007$), lower back pain ($p<0.001$), muscle pain ($p=0.023$) was more frequent, and sedimentation values were higher ($p=0.044$). *Brucella spp*. were isolated in blood cultures in fourteen (23.30%) and in abscess cultures in two (3.30%) of cases with spondylodiscitis.

Three (5%) cases had single vertebra involvement, 34 (56.70%) had two vertebra involvement and 23 (38.30%) had ≥3 vertebra involvement. Lumbar region involvement was most common (23 cases, 38.30%), followed by thoracic region (13 cases, 21.70%) and lumbosacral region (11 cases, 18.33%). Abscess was detected in 21 (35%) cases, 10 of which were paravertebral abscess, 6 were epidural abscesses, and 5 were epidural+paravertebral abscesses. Three (5%) cases had radiculitis. In cases developing spondylodiscitis, doxycycline 200 mg/day, rifampicin 600 mg/day, streptomycin 1 gr/day, ciprofloxacin 1 gr/day, trimethoprim-sulfamethoxazole 1600 mg-320 mg/day, and double or triple combinations of various antibiotics were used in treatment. The main treatment were doxycycline + rifampicin (DR), doxycycline + streptomycin (DS), doxycycline + rifampicin + streptomycin (DRS), doxycycline + rifampicin + ciprofloxacin (DRC) and doxycycline + rifampicin + trimethoprim-sulfamethoxazole (DRTS). Seventeen (28.30%) cases were given two-antibiotic treatment, while 43 (71.70%) cases were given three-antibiotic

treatment. All patients completed the recommended treatment. Three-antibiotic treatment were found to be more successful (p=0.001). Table 2 shows evaluation of two (DR, DS) and three antibiotics treatment (DRS, DRC, DRTS).

Table 1. Comparison of demographic, clinical and laboratory features of brucellosis cases

		Cases with spondylodiscitis n=60 (28.3%)	Cases without spondylodiscitis n=152 (71.7%)	Total n=212	P
Age		58.2±12.7	44.9±14.6	48.6±15.3	0.118[a]
History of contact with animals		14	31	45 (21.2%)	0.637[b]
Consumption of unpasteurized milk		17	46	63 (29.7%)	0.782[b]
Duration of symptoms	Acute	27	104	131 (61.8%)	0.007[b]
	Subacute	24	34	58 (27.4%)	
	Chronic	9	14	23 (10.8%)	
Previous brucellosis		4	20	24 11.3(%)	0.179[b]
Signs and symptoms					
Fever		26	84	110 (51.9%)	0.117[b]
Lower back pain		50	40	90 (42.5%)	**<0.001[b]**
Back pain		45	15	60 (28.3%)	0051[b]
Arthralgia		25	79	104 (49.1%)	0.176[b]
Muscle pain		10	49	59 (27.8%)	**0.023[b]**
Weight loss		9	19	28 (13.2%)	0.628[b]
Sweating		29	61	90 42.5(%)	0.276[b]
Weakness		35	73	108 (50.9%)	0.176[b]
Hepatomegay		9	17	26 (12.7%)	0.445[b]
Splenomegaly		6	21	27 (12.7%)	0.453[b]
Lymphadenopathy		2	14	16 (7.5%)	0.144[b]
Laboratory findings					
Standart Wright		436.6±6	455.3±5	444±3	0.786[a]
Erythrocyte sedimentation rate		57.2±30.2	33.625±30	40,3±28.6	**0.044[a]**
Leukocyte		7270.2±2272.8	6972.5±3996.2	7056±3590.4	0.125[a]
Hemoglobin		12.1±2.1	12.5±2.1	12.6±2.1	0.871[a]
Neutrophil		4438.7±1813.9	41189.7±3544.4	4260,1±3150	0.303[a]
Lymphocyte		2075.7±718.4	2218±817.9	2178.2±792	0.318[a]
Blood culture growth		14	28	38 (17.9%)	0.197[b]
Sacroileitis		2	13	15 (7.1%)	0.182[b]

[a] Mann Whitney U test. [b] Chi-square test

Table 2. Evaluation of two and three antibiotic combination regimen

Combination regimen	Number (%)	Response, n(%)	Nonersponse, n(%)	P
Two antibiotic	17	7 (41.2%)	10 (58.8%)	**0.001[a]**
Three antibiotic	43	36 (83.7%)	7 (61.3%)	

[a] Chi-square test

The most common combination regimen was DRS (31 cases, 51.70%). This was followed by DR treatment (14 cases, 23.30%). The failure rate was higher in the DR group (57.10%) in terms of clinical and radiological improvement (p=0.006). The mean treatment duration of the cases was 19.7±12 weeks (minimum 12-maximum 66 weeks). The success of various treatment regimens is evaluated in Table 3.

Table 3. Evaluation of the success of treatment regimens

Therapy	Number (%)	Response, n(%)	Nonresponse, n(%)	P
DR	14	6 (42.9%)	8 (57.1%)	**0.006[a]**
DS	3	1 (33.3%)	2 (66.7%)	0.131[a]
DRS	31	25 (80.6%)	6 (19.4%)	0.111[a]
DRC	8	7 (87.5%)	1 (12.5%)	0.286[a]
DRTS	4	4 (100%)	0 (%0)	0.193[a]
Toplam	60	43 (71.7%)	17 (28.3%)	-

[a] Chi-square test

Five (8.30%) cases developed relapses. Only two of them developed spondylodiscitis in relapse. Three (5%) cases developed muscle strength loss and neurological deficits, and two of them underwent surgical intervention. Five (8.30%) cases had chronic pain, and 1 (1.70%) case had difficulty walking. Physical therapy and rehabilitation programs were applied to these cases. There were no cases resulting in death.

Discussion

In this study, risk factors, clinical features and follow-up results of brucellosis spondylodiscitis cases followed up in a tertiary health institution between 2009-2019 were evaluated retrospectively. Two hundred and twelve cases were followed up with a diagnosis of brucellosis. The age range of the cases was 16-81 years, with a mean of 48.6 ± 15.3 years. According to the duration of the disease, 131 (61.80%) were acute, 58 (27.40%) were subacute, and 23 (10.80%) were chronic. The most common clinical findings are fever, fatigue, and joint pain. Brucellosis usually presents nonspecific findings such as fever, fatigue, sweating, hepatomegaly, and splenomegaly [1]. We found that back pain and muscle pain were more common in the spondylodiscitis group. Several studies have reported that back pain is the main symptom of spondylodiscitis, but it is not a specific symptom. Therefore, spondylodiscitis should be considered in the differential diagnosis in long-term cervical, lumbar, and sacral pain (especially in elderly patients) in endemic regions. No significant difference was found in laboratory findings other than erythrocyte sedimentation rate. Data from studies reported that the diagnostic value of routine laboratory findings in brucellosis is low [1-4].

In cases with osteoarticular involvement, the isolation rate is 23.30%. Brucellosis initially expands with bacteremia and is followed by a macrophage invasion that spreads with the expansion in these blood characteristics. Therefore, at least two or three separate peripheral blood culture sets are taken as soon as the disease is suspected. The change in blood cultures varies between 10% and 90%. Polymerase chain ratios are also a very useful procedure method when available due to the rapid procedure and high accessibility and specificity [5].

Osteoarticular involvement is one of the most common complications of brucellosis and is seen in 10% to 85% of patients in the literature. The wide ranges in reports in the literature may depend on the characteristics of the study sections, the radiological methods used, and the different diagnostic criteria [6-8]. According to the study systems, the most common involvement is in the lumbar spine (45%), followed by the thoracic (21.70%) and lumbosacral (18.20%) vertebrae. According to the literature, the lumbar vertebra is the most commonly affected region in brucellosis spondylodiscitis. This is followed by the thoracic and cervical vertebrae [9,10]. Epidural and paravertebral abscesses may develop in brucellosis spondylodiscitis. In our study, prevertebral/paravertebral abscesses were most frequently in the lumbar region in 21 cases. Kaptan et al. [11] evaluated 31 brucellosis spondylodiscitis cases, 19 of which had abscess lesions, and at the end of 12 weeks of treatment, they found that abscess-free individual clinical improvement (67% vs. 28%) and radiological regression (92% vs. 50%) were more frequently treated. The presence of an abscess should be monitored more closely to relax the nerve base [9-11]. Antimicrobial therapy plays a critical role in the treatment of brucellosis spondylitis. In our study, the most common treatment scheme in spondylodiscitis cases was DRS. Doxycycline plus rifampicin treatment has been associated with failure. Previous studies have reported that prolonged (usually 3 months) and multiple antibiotic regimens are more beneficial [12,13]. In an open, controlled, nonrandomized study of 31 patients with spinal brucellosis treated for a median of only 12 weeks, clinical response did not differ between patients receiving ciprofloxacin plus rifampicin and those receiving doxycycline plus streptomycin [14]. In another retrospective observational study, no significant difference was found between patients receiving doxycycline-streptomycin and those receiving doxycycline-rifampicin for 3 months, but treatment failure ranged from 15% to 18% [15]. In a retrospective cohort study conducted on 100 patients with Brucella spondylitis, the triple antibiotic regimen of doxycycline, trimethoprim-sulfamethoxazole and rifampicin was found to be more successful in the treatment of Brucella spondylitis compared to the dual antibiotic regimen of trimethoprim-sulfamethoxazole and rifampicin [16]. Many clinicians prefer the triple antibiotic regimen for the treatment of Brucella spondylodiscitis.

Three cases developed muscle weakness and neurological deficits, and two of these cases underwent surgery. Surgical treatment is indicated in patients with bone deformities and neurological compression symptoms. Surgical intervention may also be required in patients with large paravertebral abscesses and those who do not respond to antimicrobial treatment [3]. When evaluated in terms of sequelae, 5 cases had chronic pain and 1 case had difficulty walking. These patients were given a physical therapy and rehabilitation program. The need for multidisciplinary management of brucella spondylodiscitis cases is noteworthy.

Limitations

The limited aspect of the study is that the data was evaluated according to the records in the electronic patient files since it was planned retrospectively. Another limited aspect is that a relatively small number of cases were included because it was a single-center study.

Conclusion

Brucellar spondylodiscitis is a not uncommon involvement of the disease. In most cases, more than one vertebral involvement was affected. Treatment regimens containing three antibiotics were found to be more successful than regimens containing two antibiotics. Cases with muscle weakness and neurological deficits as complications were identified. A team consisting of infectious diseases, radiologists, neurosurgeons and physical therapy specialists may be useful for the treatment of spondylodiscitis.

Conflict of interest: The authors declare that they have no conflict of interest.

Author contribution		Author initials
SCD	Study concept and design	ŞÇ, İD
AD	Acquisition of data	ŞÇ, İD, AA
AID	Analysis and interpretation of data	AA, ST
DM	Drafting of manuscript	ŞÇ, AA, HC
CR	Critical revision	ST, ŞÇ, HC

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