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Osteoarticular Involvement and Inadequate Treatment of Brucellosis are Related to Relapse

Brusellozda Osteoartiküler Organ Tutulumu ve Yetersiz Tedavinin Relaps ile İlişkisi

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Abstract

Introduction: The goal of treatment in brucellosis is to control symptoms to prevent the development of complications and relapse of infection. The aim of this study was to evaluate the risk factors for relapse in brucellosis patients, including those with complications.
Materials and Methods: Our study was performed retrospectively with data from three centers. Complication of brucellosis was defined as the involvement of specific anatomical regions in the disease. Recurrence of symptoms and signs of brucellosis six months after termination of treatment and increased standard tube agglutination titer under treatment or isolation of *Brucella* spp. in sterile body fluids was defined as relapse. Inadequate treatment duration was defined as a treatment duration of less than eight weeks in patients with osteoarticular complications and less than six weeks in other brucellosis involvement. A multivariate logistic regression model was built with the variables determined to be effective in relapse development. The logistic regression model included gender, the presence of osteoarticular complications, inadequate treatment duration, treatment combinations, and leukocyte count. The SPSS 20 statistical package program was used for statistical analysis.
Results: A total of 1,296 patients were enrolled in the study. Their median age was 42 (31-54) years and 631 (48.7%) were female. One or more complications were detected in 448 (34.6%) cases. A two-drug antibiotic combination was given to 1,125 (86.8%) patients and 171 (13.2%) were treated with a three-drug antibiotic combination regimen. Three hundred sixteen (24.4%) of the patients were treated with combination therapies that included an aminoglycoside. Relapse occurred in 110 (8.5%) patients, and treatment was inadequate for 105 (8.1%) cases. Osteoarticular complications were more frequent in patients with relapse than in those without relapse (33.6% vs 18.5%, p<0.001). The presence of osteoarticular complications [odds ratio (OR): 2.413, 95% confidence interval (CI): 1.550-3.756] and inadequate treatment duration (OR: 2.861, 95% CI: 1.645-4.974) were associated with a higher rate of brucellosis relapse, while combination therapies including an aminoglycoside (OR: 0.432, 95% CI: 0.249-0.752) was associated witha lower relapse rate.
Conclusion: Our results indicate that in patients with osteoarticular complications, treatment should be administered for the recommended optimal duration, and combination therapies including aminoglycosides should be chosen preferentially in order to prevent a relapse of infection.
Keywords: Inadequate treatment, brucellosis, osteoarticular involvement, relapse

Öz

Giriş: Brusellozda tedavinin amacı semptomları kontrol etmek, komplikasyon gelişimini ve tekrarlayan enfeksiyonları önlemektir. Bu çalışmanın amacı, bruselloz hastalarında komplikasyon olanlar da dahil olmak üzere relaps için risk faktörlerini değerlendirmektir.
Gereç ve Yöntem: Çalışmamız retrospektif olarak üç merkezden alınan verilerle yapıldı. Bruselloz komplikasyonu, spesifik anatomik bölgelerin tutulumu olarak tanımlandı. Bruselloz ile ilişkili semptom ve bulguların tedavinin sonlandırılmasından altı ay sonra tekrarlaması ve tedavi altında artmış standart tüp aglütinasyon titresi veya steril vücut sıvılarında *Brucella* spp. izolasyonu relaps olarak tanımlandı. Yetersiz tedavi süresi osteoartiküler komplikasyon saptanan olgularda sekiz hafta altında, diğer bruselloz olgularında ise altı hafta altında tedavi olarak tanımlandı. Nüks gelişiminde etkili olduğu belirlenen değişkenlerle bir "multivariate" lojistik regresyon modeli oluşturuldu. Lojistik regresyon modeline cinsiyet, osteoartiküler komplikasyon varlığı, tedavi süresi uygunsuzluğu, tedavi kombinasyonları ve lökosit sayısı dahil edildi. İstatistiksel analiz için SPSS 20 istatistik paket programı kullanıldı.

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Öz

Bulgular: Toplam 1.296 hasta çalışmaya dahil edildi. Hastaların yaş ortancası 42 (31-54); 631'i (%48,7) kadın idi. Olguların 448'inde (%34,6) bir veya daha fazla komplikasyon tespit edildi. Hastaların 1.125'ine (%86,8) iki ilaç antibiyotik kombinasyonu verildi ve 171'ine (%13,2) üç ilaç antibiyotik kombinasyonu uygulandı. Üç yüz on altı (%24,4) hastaya bir aminoglikozid içeren kombinasyon tedavi uygulandı. Relaps 110 (%8,5) hastada meydana geldi ve tüm hastaların 105'inde (%8,1) tedavi yetersizdi. Osteoartiküler komplikasyonlar nüks olanlarda nüks olmayanlara göre daha sık bulunmuştur (%33,6-18,5, p<0,001). Bruselloz olgularında osteoartiküler komplikasyon varlığının [odds oranı (OR): 2,413 güven aralığı (CI): 95; 1,550-3,756] ve uygunsuz tedavi süresinin [OR: 2,861 (CI: 1,645-4,974)] relaps enfeksiyon gelişimini artırdığı, aminoglikozid içeren tedavi kombinasyonlarının [OR: 0,432 (CI: 0,249-0,752)] ise relaps gelişimini azalttığı tespit edildi.
Sonuç: Sonuçlarımız osteoartiküler komplikasyonları olan hastalarda tedavinin önerilen optimal süre boyunca uygulanması gerektiğini ve enfeksiyonda relaps gelişimini önlemek için aminoglikozidleri içeren kombinasyon tedavilerinin tercih edilmesi gerektiğini göstermektedir.
Anahtar Kelimeler: Yetersiz tedavi, bruselloz, osteoartiküler tutulum, relaps

Introduction

Brucellosis is a systemic disease that can manifest along a highly heterogeneous clinical spectrum and involve many different organs in humans[1].The goal of treatment in brucellosis is to control symptoms toprevent the development of complications and relapse of infection[2]. Relapse, defined as *Brucella* culture positivity and/or recurrence of disease signs and symptoms after termination of treatment, occurs in about 5-30% of cases[2,3]. There are many studies evaluating the influence of combination therapies and treatment duration on brucellosis relapse rates. Most of these studies were conducted to determine the optimal combination therapy and treatment duration for uncomplicated cases[2-5]. However, there are few studies evaluating the relationship between complications and infection relapse[2,6]. The aim of this study was to evaluate the risk factors for relapse in brucellosis patients, including those with complications.

Materials and Methods

The study was conducted by retrospectively evaluating records from the infectious disease inpatient units and outpatient clinics of Erzurum Training and Research Hospital, Gaziantep Dr. Ersin Arslan Training and Research Hospital, and Mardin State Hospital. As it was a retrospective, cross-sectional study that did not constitute an additional risk to the patient, additional ethics committee approval was waived. The demographic data, laboratory results, radiological examination records, electronic prescription information, and follow-up records of patients who were registered in the hospital computer database with a brucellosis diagnostic code (International Statistical Classification of Diseases and Related Health Problems=ICD codes; A23.0, A23.1, A23.2, A23.3, A23.4, A23.8, A23.9) between January 1, 2013 and December 31, 2016 were included in the study. The patients were grouped as those who had relapse and those who did not, and the groups were compared in terms of demographic data, laboratory findings at the time of initial diagnosis, and treatment approaches and durations. Those who matched the ICD code but did not meet the diagnostic criteria and patients under the age of 18 were excluded.

Definitions

Brucellosis was defined as the presence of microbiological evidence together with clinical signs and symptoms. Patients who met at least one of the following criteria were included in the study[4,7]:

1. Isolation of *Brucella* spp. in sterile body fluids,

2. Titer ≥1/160 ina*Brucella* standard tube agglutination test (SAT),

3. Titer ≥1/320 in a *Brucella* tube agglutination with Coombs,

4. A minnimum 4-fold increase in SAT titer in serial tests performed two-three weeks apart.

The Cromatest (Linear chemicals, Spain) kit for *Brucella* SAT, and the Metser (Metserlab, İstanbul) Coombs *Brucella* test kit for *Brucella* Coombs gel test were used. *Brucella* immunoglobulin G (IgG) and IgM antibody concentrations were tested with ELISA kits from VirCell (VirCell, Spain). The BACTEC™ FX (BD, United States) blood culture system for detecting *Brucella* bacteremia within the routine 1-week incubation period was used. Two-mercaptoethanol was not used in the diagnosis of brucellosis. *Brucella* species were not defined according to subtypes, and bone marrow culture was not performed.

Complication: Defined as clinical or physical examination findings associated with disease involvement of specific anatomical regions and laboratory or radiological evidence thereof.

Osteoarticular complication: Defined as the detection of inflammation in one or more vertebrae (±discs) or in the joint region by radiological or/and scintigraphic methods[4,8].

Hematopoietic complication: In the absence of any other describable etiology, a platelet count <150.000 IU/ml was accepted as thrombocytopenia, a leukocyte count <4000 IU/

ml as leukopenia, and a hemoglobin level <12 g/dl in females and <13 g/dl in males as anemia. The detection of all three of these findings (anemia, leukopenia, and thrombocytopenia) was considered pancytopenia, and the presence of any two of them was considered bicytopenia[7].

Hepatobiliary complication: In the absence of any other identifiable etiology, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels >5 times the normal value (NV) were accepted as hepatitis, while alkaline phosphatase (ALP) level ≥1.5 times the NV, gamma-glutamyl transferase (GGT) level ≥3 times the NV, or total bilirubin values >2 mg/dl was considered cholestasis. In radiologic evaluation examination (abdominal ultrasonography or computed tomography), liver size >16 cm (in the midclavicular line) and spleen size >13 cm were assessed as hepatomegaly and splenomegaly, respectively[7,9].

Genitourinary complication: Detection of testicular-epididymal pain and positive ultrasonography findings (epididymis with an enlarged, hypoechoic heterogeneous appearance, abscess formation, and bilateral involvement) were accepted as epididymo-orchitis[7,10,11].

Neurological complication (neurobrucellosis): Defined as the presence of neurological symptoms together with *Brucella* SAT positivity at any titer or the isolation of *Brucella* spp. in cerebrospinal fluid.

Cardiac complication: Cardiac complications of brucellosis include endocarditis, myocarditis, pericarditis, and pancarditis. Endocarditis is the most common cardiovascular complication. The definitive diagnostic criteria for brucella endocarditis were defined according to Duke's criteria[12,13].

Relapse: Inpatients diagnosed with and treated for brucellosis, relapse was defined as the recurrence of symptoms and signs associated with brucellosis and at least one of the following findings at least six months after termination of treatment[2,8]:

- Increase in SAT titer that was previously reduced with treatment,

- Repeat of *Brucella*spp. isolation in sterile body fluids.

Inadequate treatment duration: Defined as treatment duration of less than eight weeks in patients with osteoarticular complications and less than six weeks in other brucellosis conditions[14].

Statistical Analysis

The SPSS version 20 software package was used for statistical analyses. The Kolmogorov-Smirnov test was used to test the conformity of continuous variables to normal distribution. Comparisons of two independent groups were made using Mann-Whitney U test for non-normally distributed variables. Relationships between categorical variables were tested with chi-square analysis. Univariate analyses were performed first for groups of patients with and without relapse. Multivariate analysis was then performed on variables with a significance level below 0.20. Multivariate logistic regression was used as the analysis method. The logistic regression model included variables that were believed to influence the development of relapse and showed significant differences between groups: sex, the presence of osteoarticular complications, inadequate treatment, treatment combinations, and leukocyte white blood cells (WBC) (cut off point=4000 IU/ml) count. Although a significant difference in treatment duration was detected in univariate analysis, it was not included in the model due to its correlation with treatment inadequacy. Descriptive statistics were expressed as frequencies, percentages (%) and median (25-75 percentiles). Multicollinearity was measured by variance inflation factors (VIF) and tolerance. VIF values were less than 3.0 and tolerance more than 0.2, so there was no problem with multicollinearity. A p value of <0.05 was regarded as statistically significant.

Results

A total of 1,296 patients were included in the study. The median age of the patients was 42 (31-54) years; 631 (48.7%) patients were female and 665 (51.3%) were male. Of these, 963 patients (74.3%) had positive *Brucella* SAT results (≥1/160) and 1,081 (83.4%) had positive *Brucella* Coombs gel test results (≥1/320). Of the patients with <1/160 titers in the *Brucella* SAT, 331 (25.5%) tested positive in the *Brucella* tube agglutination with Coombs. *Brucella* was isolated in the blood cultures of 13 patients (1.0%). However, blood culture was applied to only 76 (5.8%) of our patients. *Brucella* was isolated in 13/76 (17.1%) patients in whom blood cultures were performed. One patient was diagnosed by positive blood culture despite negative tube agglutination test results. *Brucella canis* was isolated from the blood culture in this case. *Brucella* antibodies were studied by ELISA only in 209 (16.1%) of the patients, and all of them were positive for IgM and/or IgG antibodies.

One or more complications were detected in 448 (34.6%) of the cases. Osteoarticular complications occurred in 258 (19.8%), hematopoietic in 159 (12.3%), hepatobiliary in 96 (7.4%), genitourinary in 19 (1.5%), cardiac in one (0.07%), and neurological in one (0.07%) cases. In order to detect osteoarticular complications, bone scintigraphy was performed in 16 (6.2%) and spinal magnetic resonance imaging in254 (98.4%) cases. None of the patients died. The distribution of complications is presented in Table 1.

The distribution of antibiotic combinations is presented in Table 2. Gentamicin was not the preferred drug because streptomycin was in habitual use in brucellosis treatment,and it was used intramuscularly once a day, which facilitated drug

administration. Treatment duration was less than six weeks for 72 (5.6%) patients, six weeks for 622 (48.0%), and over six weeks for 602 (46.5%) patients. Treatment duration was longer in patients with complications (median: 70 days, range: 56-84 days) compared with uncomplicated cases (median: 42 days, range: 42-56) (p<0.001). Treatment duration was inadequate for 105 (8.1%) of the patients.

Relapse occurred in 110 (8.5%) patients. In blood culture, which wasobtained from only two of the patients who developed relapse, there was no growth of *Brucella*. Relapse developed after a mean of 572.7±358.6 days and a median of 468 (189-2254) days. A comparison of patients with and without relapse in terms of demographic features,the presence of complications, and laboratory parameters at the time of diagnosis is shown in Table 3. The number of patients receiving treatment between six weeks and three months was 629 (48.5%), 477 (36.8%) of received treatment for three months to six months, and 88 (6.6%) received treatment for more than 6 months.

Data obtained from the multivariate logistic regression model evaluating risk factors in terms of relapse development are given in Table 4. The presence of osteoarticular complications [odds ratio (OR): 2.413, 95% confidence interval (CI): 1.550-3.756] and inadequate treatment duration (OR: 2.861, 95% CI: 1.645-4.974) were associated with a higher rate of brucellosis relapse, while combination therapies including an aminoglycoside (OR: 0.432, 95% CI: 0.249-0.752) was associated with a lower rate.

Table 1. Distributions of complication in brucellosis

Complication distributions	n (%)
Osteoarticular complications	256 (19.8)
Spondylitis	51 (19.8)
Spondylitis + Psoas abscess	4 (1.6)
Spondylitis + sacroiliitis	11 (4.3)
Bilateral sacroiliitis	122 (47.2)
Unilateral sacroiliitis	51 (19.7)
Knee involvement + bilateral sacroiliitis	2 (0.8)
Knee involvement	16 (6.2)
Shoulder involvement	1 (0.4)
Hematopoietic complications	159 (12.3)
Anemia	42 (26.4)
Leukopenia	16 (10.0)
Thrombocytopenia	52 (32.7)
Bicytopenia	28 (17.6)
Pancytopenia	21 (13.2)
Hepatobiliary complication	96 (7.4)
ALT >5 times the NV	15 (15.6)
Total bilirubin >2 mg/dl	3 (3.1)
ALP ≥1.5 times the NV or GGT ≥3 times the NV	8 (8.3)
Hepatomegaly or splenomegaly	70 (72.9)
Genitourinary complications	19 (1.5)
Cardiac complications	1 (0.07)
Neurological complications	1 (0.07)

NV: Normal value, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase

Discussion

The relapse rate in patients with brucellosis varies between 2.4% and 29.0%[2,3,5,6,15-17]. The relapse rate in our study was 8.5%, which is consistent with the literature data. It has been shown thatthetotal treatment duration in particular is a determining factor for infection relapse and that short-term treatment approaches (≤1 month) increases the relapse rate independent of the combination therapy used[3-5]. Sofian et al.[18] showed in a randomized controlled trial that extending treatment beyond six weeks does not affect the development of infection relapse in uncomplicated cases. The World Health Organization (WHO) recommends six weeks of treatment for uncomplicated brucellosis and at least eight weeks of treatment in patients with osteoarticular complications[14]. However, there is no consensus in the literature regarding the optimal treatment approach for complicated cases. In a study carried out by Kayaaslan et al.[8], treatment duration for brucellosis patients with osteoarticular involvement ranged between four and six months. In a study by Kaptan et al.[19], patients with *Brucella* spondylodiscitis underwent treatment for 12-39 weeks. It has been reported that continuation of treatment for 24 weeks or longer can provide effective treatment for patients with spondylodiscitis[20]. However, in our study, the effect of treatment prolongation after three months of treatment in patients with osteoarticular complications on relapse was not detected. In a 16-year prospective study examining the risk factors of recurrence in Brucellosis patients, "less effective" antibiotic therapy was found to be an independent risk factor for relapse. Treatment periods (in the same treatment regimens) were observed to be

Table 2. Distribution of antibiotic combinations

Antibiotic combination	n (%)
Two-drug antibiotic combination	**1125 (86.8)**
Doxycycline + rifampicin (DR)	930 (71.8)
Doxycycline + streptomycin (DS)	161 (12.4)
Doxycycline + ciprofloxacin (DC)	15 (1.2)
Other Combinations	19 (1.4)
Three-drug antibiotic combination	171 (13.2)
Doxycycline + rifampicin + streptomycin (DRS)	150 (11.6)
Doxycycline + rifampicin + ciprofloxacin (DRC)	9 (0.7)
Doxycycline + streptomycin + ciprofloxacin (DSC)	5 (0.4)
Other combinations	7 (0.6)

Table 3. Comparison of brucellosis patients with and without relapse

Characteristic	Relapse (+) (n=110)	Relapse (-) (n=1186)	p value
Age, years	46.0 (33-55)	42.0 (30-53)	0.086*
Female	52 (47.3%)	579 (48.8%)	0.756**
Complications	52 (47.3%)	396 (33.4%)	**0.003****
Osteoarticular complications	37 (33.6%)	220 (18.5%)	**<0.001****
Hematopoietic complications	11 (10.0%)	148 (12.5%)	0.448**
Hepatobiliary complications	11 (10.0%)	85 (7.2%)	0.278**
Genitourinary complications	1 (0.9%)	19 (1.6%)	0.587**
Treatment			
Osteoarticular complications and 3 to 6-month treatment duration	12 (10.9%)	102 (86.0%)	0.420**
Osteoarticular complications and >6-month treatment duration	3 (0.2%)	23 (19.3%)	
AG	17 (15.5%)	299 (25.2%)	**0.023****
Non-AG	93 (84.5%)	839 (74.8%)	
Non-AG (2-drug combination)	91 (9.4%)	873 (90.6%)	**0.025****
AG (3-drug combination)	7 (4.5%)	148 (95.5%)	
Combination therapy			
2-drug combination therapy	98 (89.1%)	1027 (86.6%)	0.459**
3-drug combination therapy	12 (10.9%)	159 (13.4%)	
Treatment duration*** (day)	42 (42-70)*	56 (42-84)*	**0.021***
Inappropriate treatment	20 (19.0%)	90 (7.6%)	**<0.001****
WBC (10^3/L)	6415 (5412-7825)	6800 (5699-8202)	0.090*
HGB (g/dL)	14.6 (13.1-15.4)	14.3 (13.3-15.4)	0.570*
PLT (10^3/L)	253250 (203500-289000)	254050 (206000-309975)	0.302*
ALT (U/L)	22 (16-35)	22 (17-389)	0.641*
AST (U/L)	23 (18-37)	23 (18-34)	0.574*
Creatinine (mg/dL)	0.7 (0.6-0.8)	0.7 (0.6-0.8)	0.730*
CRP (mg/dL)	4.0 (3.0-13.5)	5 (3.0-19.0)	0.339*
Erythrocyte sedimentation rate (h)	12.5 (5.0-23.5)	12.0 (4.0-25.0)	0.582*

*Mann-Whitney U test, **Chi-square test, ***Median (25^{th}-75^{th} percentile).

AG: Aminoglycoside, Non-AG: Non-aminoglycoside, WBC: White blood cells, HGB: Hemoglobin, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, PLT: Platelet, CRP: C-reactive protein.

Non-AG (2-drug combination):Used brucella effective two drug combination but not AG; AG (3-drug combination) aminoglycoside-containing brucella effective combination of three drugs

Table 4. Logistic regression model based on relapse development

	B	S.E.	Significance (p)	OR	95% CI
Gender (male)	0.141	0.204	0.49	1.151	0.720-1.718
Combination therapy with AG	-0.838	0.282	0.003	0.432	0.249-0.752
Patients with inadequate treatment	1.051	0.282	0.001	2.861	1.645-4.974
Patients with osteoarticular complications	0.881	0.226	0.001	2.413	1.550-3.756
WBC (<4000 10^3/L)	0.001	0.001	0.106	1.000	1.000-1.000

AG: Aminoglycoside, WBC: White blood cells, B: xxxxxxx, S.E.: Standard error, OR: Odds ratio, CI: Confidence interval

shorter in the less effective group[21]. Similarly, in our study, treatment inadequacy was defined according to the treatment durations recommended by the WHO, and short-term treatment was associated with a 2.86-fold higher relapse rate.

In the study performed by Ariza et al.[21], 41 of 131 patients in the group defined as the group receiving less effective treatment had a short treatment period (30 days). This was associated with relapse. In this study with 530 patients, the incidence of inappropriate treatment time was 7.7%. In our study, this

frequency was found to be 8.4% (110/1296). This was because patients living in the regions where the study was conducted did not apply to the hospital for further treatment.

In addition to the treatment duration, the drugs used and their combinations also had a direct effect on the rate of infection relapse. In November 2006, a consensus meeting aimed at reaching a common specialist statement on the treatment of brucellosis was held in Ioannina. The antibiotic regimen containing aminoglycoside was considered as the gold standard for treatment[22]. There are also studies showing that aminoglycoside combination therapies reduced the rate of relapse[2,5,23]. A Cochrane meta-analysis published in 2012 showed that doxycycline and streptomycin combination therapy was associated with a lower rate of treatment failure and infection relapse compared with doxycycline and rifampicin therapy[24]. The results of a meta-analysis by Meng et al.[25] demonstrated that compared with streptomycin, a rifampicin combination in patients receiving doxycycline back-bone therapy was associated with a higher rate of treatment failure and relapse. The Ministry of Health's action plan of zoonotic diseases emphasized that the combination of streptomycin and doxycycline had a lower relapse rate than the combination without streptomycin[26]. Similarly, patients in our study treated with aminoglycoside combination therapies (independent of the other agents in the combination) had a lower relapse rate.

There are few studies in the literature evaluating the relationship between complications and brucellosis relapse. Aygen et al.[6] detected no significant relationship between relapse and the development of complications. Similarly, in a retrospective study of 980 cases of brucellosis, Roushan et al.[2] observed no relationship between the presence of complications and relapse. Contrary to the data in the literature, our results showed that the presence of osteoarticular complications was associated with a 2.4-fold higher relapse rate. Osteoarticular involvement was the only complication significantly associated with relapse.

Although complications vary in frequency, site of involvement, and presentation, osteoarticular complications are reported to be the most common type of complication in patients with brucellosis[8,14,27]. In a systematic review evaluating Brucellosis patients in Turkey, Calik and Gokengin[1] reported the rate of osteoarticular complications to be 43.74% (n=1839). Kayaaslan et al.[8] determined the rate of osteoarticular complications as 22% in a study including 700 patients. At a rate of 19.8%, osteoarticular complications were also the most common in our study.

Independent risk factors that increase the risk of relapse, such as initial symptoms (such as fever >38 °C) and duration of symptoms before therapy have been reported in the literature. Also, blood culture positivity, which may cause more aggressive disease, is an independent risk factor for relapse. Blood culture positivity sometimes occurs before symptoms. The prolongation of the period between the development of the disease and the onset of treatment decreases the frequency of blood culture positivity[21,28]. In addition, focal complications, due to the low number of *Brucella* in the blood, may limit the detection of relapse cases[29]. On the other hand, it is possible to diagnose false-positive relapses with antibody tests that are positive for a long time. In such cases, diagnosis of relapse brucellosis by polymerase chain reaction assay can be promising[30]. In our study, the relapse status of the initial findings were questioned then recorded as present or absent. However, the initial symptoms of all brucellosis patients were not recorded in detail. Therefore, the relationship between initial symptoms and relapse could not be investigated. This is the most important limitation of our study.

Conclusion

In conclusion, brucellosis patients must be evaluated carefully for the development of osteoarticular complications because these are the most common complications, the optimal treatment duration is not clear, and they are associated with an increased risk of relapse. Our results indicate that in patients with osteoarticular complications, treatment should be administered for the recommended optimal duration, and combination therapies including aminoglycosides should be selected in order to prevent infection relapse.

Ethics

Ethics Committee Approval: The ethics committee approval was not received. Because the article is retrospective.

Informed Consent: Retrospective study.

Peer-review: Externally and internallypeer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.Y., Ö.K., H.S.Ö., Concept: M.D., Design: M.D., H.S.Ö., Data Collection or Processing: H.S.Ö., Ö.K., Y.Y., Analysis or Interpretation: H.S.Ö., Literature Search: H.S.Ö., Ö.K., Writing: H.S.Ö., Ö.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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