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ORİJİNAL ARAŞTIRMA

Brucellosis: Are There Any Affect of Bacteremia on Clinical Outcome

Bruselloz: Bakteriyeminin Klinik Sonuca Etkisi Var mı?

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ABSTRACT

Aim: In our study, we aimed to evaluate the epidemiological, clinical, serological and prognostic features of bacteremic and non-bacteremic brucellosis based on our clinical experience in patients presenting with brucellosis.

Material and Method: The study was carried out retrospectively in two different hospitals providing tertiary health care in Turkey. The data were obtained from the hospital information network of the centers. Patients over the age of 18 who were diagnosed with brucellosis during screening and hospitalized were included in the study.

Results:The data of 422 patients were included in the study. While 170 patients had positive culture results for Brucella spp, the results of 252 patients for Brucella spp. were negative. The number of patients with fever was higher in bacteremic patients (P= 0.035). Significant elevation of AST (P<0.001), ALT (P<0.001), CRP ((P=0.003) levels, leukopenia (P=0.006), and pancytopenia (P=0.006) were detected in bacteremic patients. The existence of complications was 50.4% in nonbacteremic patients and 38.2% in bacteremic patients (P=0.014). Agglutination titers of 1/1280 or greater were detected in 129 (51.2%) culture negative and 106 (62.4%) culture-positive cases (P=0.024). In multivariate analysis, leukopenia and elevated AST level were found to be the predictor of bacteremia in patients. Commonly used antimicrobial regimens consisted of doxycycline plus streptomycin or doxycycline plus rifampicin given for 6 weeks. The most common way of transmission (68.2%) was the ingestion of milk products from diseased animals.

Conclusion: Bacteraemia was detected in 40.3 % of patients. The existence of bacteremia was positively correlated with fever, higher levels of ALT, AST, CRP leukopenia, and pancytopenia, and inversely with the rate of complication and relapses.

Keywords: Brucellosis, bacteriemia, clinical finding, laboratory finding

ÖZ

Amaç: Çalışmamızda bakteriyemik ve bakteriyemik olmayan brusellozun epidemiyolojik, klinik, serolojik ve prognostik özelliklerini bruselloz ile başvuran hastalardaki klinik deneyimlerimize dayanarak değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışma, Türkiye'de üçüncü basamak sağlık hizmeti veren iki farklı hastanede retrospektif olarak gerçekleştirildi. Veriler merkezlerin hastane bilgi ağından elde edildi. Tarama sırasında bruselloz tanısı alan ve hastaneye yatırılan 18 yaş üstü hastalar çalışmaya dahil edildi.

Bulgular: Çalışmaya 422 hastanın verileri dahil edildi. Brucella spp. için 170 hastanın kültür sonucu pozitif bulunurken, 252 hastanın Brucella spp. olumsuzdu. Bakteriyemik hastalarda ateşi olan hasta sayısı daha fazlaydı (P= 0.035). Bakteriyemik hastalarda AST (P<0.001), ALT (P<0.001), CRP ((P=0.003), lökopeni (P=0.006) ve pansitopeni (P=0.006) düzeylerinde anlamlı yükselme saptandı. bakteriyemik olmayan hastalarda %50,4 ve bakteriyemik hastalarda %38,2 (P=0,014) 129 (%51,2) kültür negatif ve 106 (%62,4) kültür pozitif olguda 1/1280 ve üzeri aglütinasyon titresi saptandı (P=0,024)) Çok değişkenli analizde lökopeni ve yüksek AST düzeyi hastalarda bakteriyeminin öngördürücüsü olarak bulundu.Sık kullanılan antimikrobiyal rejimler doksisiklin + streptomisin veya doksisiklin + rifampisinden oluşuyordu ve 6 hafta süreyle verildi.En yaygın bulaşma yolu (%68.2) hastalıklı hayvanlardan elde edilen süt ürünlerinin yenmesiydi.

Sonuç: Hastaların %40.3'ünde bakteriyemi saptanmıştır. Bakteriyeminin varlığı ateş, yüksek ALT, AST, CRP lökopeni ve pansitopeni ile pozitif, komplikasyon ve nüks oranı ile ters orantılıydı.

Anahtar Kelimeler: Brusellozis, bakteriyemi, klinik bulgular, laboratuar bulgular

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INTRODUCTION

Brucellosis is an endemic disease of zoonosis in countries that are engaged in animal husbandry. İt has a highly contagious character for the transition from animal to human. The mortality rate is low, but the morbidity rate is high and it causes loss of workforce in patients. The infectious agent is mostly transmitted by the consumption of infected milk and dairy products. İt shows variable Clinic manifestations from systemic infection to simple weakness. Definitive diagnosis is the isolation of bacteria from blood and/or other specimen. However, culturing the causative agent is difficult and takes time. Waiting for the culture result delays the treatment. In addition, patients can apply to different polyclinics and receive antibiotic treatment before diagnosis. If antibiotics are used, they can suppress the bacteria and prevent its growth in culture. These difficulties in diagnosis can be solved by evaluating serology and non-specific laboratory tests together with a good anamnesis and examination findings. In our study, we aimed to evaluate the clinical, serological and other laboratory parameters of brucellosis patients with and without blood culture growth.

MATERIAL AND METHOD

The study was approved by Ankara City Hospital No: 1 Clinical Researches Ethics Committee (Date: 29/06/2022, Decision no: E1/2751/2022). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was carried out retrospectively with the data of Ankara Numune Training and Research Hospital for the period of January 2002-July 2014, and of the Department of Infectious Diseases and Clinical Microbiology of Kafkas University Faculty of Medicine for the period of January 2011-June 2014. Data were obtained from the hospital information network of two separate centers. Patients over the age of 18 who were hospitalized and diagnosed with brucellosis were taken into account during the screening. Outpatient clinic applications were not included in the study. Recent hospitalization data of patients with a history of multiple hospitalizations were included in the study. Other admissions are excluded.

At the end of the screening, we evaluated 422 patients with brucellosis who had blood culture and standard tube agglutination test (SAT) in the system. The patients' medical history and physical examination findings, radiological data, complete blood count (CBC), C-reactive protein (CRP) and blood chemistry (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) were recorded as non-specific laboratory data. In our case definition, patients with positive culture results were grouped as brucellosis with bacteremia and those who were diagnosed with SAT results without culture growth were grouped as brucellosis without bacteremia. The obtained data were compared between these two groups.

The criterion for duration of symptoms was classified as acute (less than 8 weeks), subacute (between 8 and 52 weeks), and chronic (more than 52 weeks) (1,2). Recurrence of clinical symptoms after discontinuation of treatment in patients who fully recovered was considered relapse. The presence of symptoms or physical manifestations of the disease in a specific anatomical region in a patient with active brucellosis was defined as a complication.

In the diagnosis of brucellosis, isolation of Brucella species in the blood (Bactec 9120; Becton Dickinson Diagnostic Instrument System, Sparks, MD, USA) and detection of specific antibodies in significant titers and/or at least a four-fold increase in antibody titer at 2- or 3-week intervals in serum samples were used. A titer of ≥ 1/160 on the SAT was considered significant.

Gram stain, oxidase test, urea test and Brucella agglutination test (RSHM Antisera, Ankara, Turkey) were used for bacterial identification. Tests used serologically are Rose Bengal plaque agglutination test (Pendik Veterinary Control and Research Institute, Istanbul, Turkey), SAT test (B abortus S99 antigen Pendik Veterinary Control and Research Institute, Istanbul, Turkey) and Coomb's test.

The diagnosis of osteoarticular complications was made by clinical findings and radiological imaging. The diagnosis of neurobrucellosis was defined as the isolation of Brucella species from CSF taken from patients with neurological disorders and/or STA positivity at any titer in CSF. For liver involvement, the absence of any other etiological condition was considered in those with a 5-fold increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels.

Statistical Analysis

PASW 18.0 for Windows was used for statistical analysis. Descriptive statistics, numbers, and percentages for categorical variables to numeric variables mean, standard deviation, median, minimum, and maximum offered. Dual independent group comparisons normal distribution assumption is not met, Mann-Whitney U test was used in the case. The chi-square for categorical variables whose condition is not met in the case of the multilateral and bilateral comparison group was used as the chi-square test statistic. A grade of 0.05 was considered a statistically significant p-value status to be small.

RESULTS

170 patients (73 female, 42.9%; 97 male, 57.1%; mean age 48.0 years) had positive culture results for Brucella spp, and 252 patients (109 female, 43.3%; 143 male, 56.7%; mean age 43 years) had negative culture results. Nonbacteremic cases were diagnosed based on symptoms suggesting brucellosis and a serological titer of 1/160 or greater. The mean age of bacteremic patients

(48.0 years) was greater than that of nonbacteremic patients (43.0 years) (p =0,173).

The potential source of infection was determined to be the consumption of unpasteurized dairy products, especially fresh cheese (n:288 %68,2), and either direct contact with animals or working with animal products (n:278 %65,9); no source was identified for 2 patients (**Table 1**). The mode of transmission did not differ in terms of production of the agent.

According to the duration of the symptoms, 260 patients applied in the acute period, 93 patients were in the subacute period and 20 patients were in the chronic period. 49 patients had previously received treatment for brucella (**Table 1**).

Of the 422 patients, 10.4% had leukopenia and 83.4% had WBC between 4,000 and 11,000 per mm³ and 6.2% had leukocytosis. A significant elevation of AST ($p < 0.001$) and ALT ($p< 0.001$) levels and leukopenia ($p=0.030$) and pancytopenia (anemia plus platelet <150000 plus WBC<4000) ($p=0.006$)were detected in bacteremic patients (**Table 2**). The existence of complications was 50.4% in nonbacteremic patients and 38.2% in bacteremic patients ($p=0.014$). The elevated

Table 1. Demographics and epidemiological characteristics of patients

	Nonbacteremic patients	Bacteremic patients	p-value
Sex (n (%))			
Male	143 (56.7)	97 (57.1)	0.949
Female	109 (43.3)	73 (42.9)	
Age (Mean±SD) (Median)	44.43±17.13 (43)	46.84±17.86 (48)	0.173
Clinic form (n (%))			
Acute	158 (62.7)	102 (60.0)	0.616
Subacute	51 (20.2)	42 (24.7)	
Chronic	11 (4.4)	9 (5.3)	
Relapse/reinfect	32 (12,7)	17 (10.0)	
Mode of transmission (n (%))			
Ingestion of unpasteurized milk	169 (67.1)	119 (70)	0.525
Direct contact with animal products or working with animal products	167 (66.3)	111 (65.3)	0.836
No source was identified (others)	1 (0.4)	1 (0.6)	-*
Existing of complication	127 (50.4)	65 (38.2)	0.014

* Analysis was not performed since several patients were not sufficient enough. SD: Standard Deviation, n:numbers of students

Table 2. Laboratory results on which the diagnosis of the patients was based

Laboratory tests		Nonbacteremic patients	Bacteremic patients	p-value
WBC count per mm³ (n (%))				
	<4000	18 (7.1)	26 (15.3)	0.006
	4000–11000	222 (88.1)	130 (76.5)	
	>11000	12 (4.8)	14 (8.2)	
Thrombocyte count per mm³ (n (%))				
	<150000	27 (10.7)	24 (14.1)	0.293
	<100000	12 (4.8)	11 (6.5)	0.448
	<50000	7 (2.8)	2 (1.2)	0.264
Hemoglobin (g/dL) Anemi (n (%))	<14 for males, <12 for females	137 (54.4)	96 (56.5)	0.670
Pancytopenia		3 (1.2)	10 (5.9)	0.006
ALT (IU/l) (Mean±SD) (Median)		35.11±34.81 (24)	58.99±66.97 (36)	<0.001
ALT > 40 IU/l (n (%))		45 (24.6)	66 (47.5)	<0.001
AST (IU/l) (Mean±SD) (Median)		38.23±39.57 (24)	55.35±63.28 (40)	<0.001
AST > 40 IU/l (n (%))		48 (26.2)	69 (49.6)	<0.001
CRP (mg/l) (Mean±SD) (Median)		364.98±423.23 (212)	462.36±467.05 (300)	0.003
CRP (mg/l) (n (%))				
	<20	119 (47.2)	62 (36.5)	0.029
	≥ 20	133 (52.8)	108 (63.5)	
CRP (mg/l) (n (%))				
	≤5	49 (19.4)	16 (9.4)	0.005
	>5	203 (80.6)	154 (90.6)	
Sedimentation (mm/h) (Mean±SD) (Median)		39.62±41.53 (31)	40.17±25.96 (36)	0.388
Sedimantation (mm/h) (n (%))				
	≤20	84 (33.6)	48 (28.4)	0.261
	>20	166 (66.4)	121 (71.6)	
	≤40	146 (58.4)	93 (55)	0.494
	>40	104 (41.6)	76 (45)	
STA (n (%))				
	≥1/160	246 (97.6)	167 (98.2)	0.667
	≥1/1280	129 (51.2)	106 (62.4)	0.024

n:Numbers of patients , WBC: White Blood Cell, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, , CRP: C-Reactive Protein, STA: Standard Tube Agglutination Test

AST and ALT levels returned to normal in all patients following treatment targeted to brucellosis.

The patients were treated with various combinations of antibiotics. All patients were initially followed up in the hospital and were discharged after their general condition improved, and were called for outpatient control at 2-week intervals. Patients were followed up to 6 months after the end of treatment.

Table 3: Comparison of risk factors in determining the presence of bacteremia

	p	OR	95,0% CI OR	
			Lower limit	Upper limit
WBC	0.036			
WBC (Low)	0.030	2.227	1.081	4.585
WBC (High)	0.117	2.281	0.814	6.394
AST>40	<0.001	2.392	1.475	3.878
CRP >5 mg/l	0.055	2.086	0.984	4.421
Absence of complications	0.056	1.583	0.988	2.537

WBC: White Blood Cell, ALT: Alanine Aminotransferase, CRP: C-Reactive Protein, CI: confidence interval, OR:Odd Ratio

In the model created with WBC, pancytopenia, ALT, AST, CRP, STA, fever, and existing complication variables, which were suitable from the comparison analyses to determine the risk factors for the presence of bacteremia, low WBC and high AST were statistically significant risk factors (respectively p= 0.030, p<0.001)(**Table 3**).

DISCUSSION

Brucella, which is common especially in developing countries, is a multisystemic zoonotic infectious disease seen in humans. It presents a wide clinical spectrum, which is clinically divided into acute, subacute, or chronic periods ranging from mild symptoms to severe symptoms (3). As it can affect any organs and body system, the symptoms are not pathognomonic and therefore can be easily confused with many other diseases, including malignancies. The antibiotics used in the treatments for these diseases partially suppress the bacteria but cannot destroy it and the patients experience a chronically uncomfortable process. (4,5,6). Therefore, it is important to confirm the diagnosis.

Among the many methods used in the diagnosis of Brucella, clinical history, physical examination, bacterial culture from various biological sources, microscopy, biochemical tests, and serology standard diagnosis systems are used. Molecular tests, which have been in demand recently, are expensive methods, and the persistence of positivity in patients whose treatment has been completed are the limitations of the test. The definitive diagnosis method is the production of the agent in blood culture. Although the sensitivity is 10-90%, taking a blood culture in cases where the disease is suspected to detect bacteremia developing after infection has an important place in the diagnosis. (7).

In this study, which evaluated only the patients whose blood culture was taken, the production rate in the blood culture of all patients was 40.3%.

Growth in culture is affected by several factors such as disease stage, previous antibiotic use, and culture technique. Bacteria are more difficult to grow in patients with chronic, organ-related diseases (8). Therefore, and also because blood culture takes time, serological methods are generally supportive in the diagnosis in case of clinical suspicion. In our study, standard tube agglutination was 1/160 and above in 97.6% of patients without bacteremia and in 98,2% of those with bacteremia.

There may also be problems in terms of diagnosis during the use of serological tests. Since serological test positivity can persist for one year or more, it may confuse non-brucellosis infections in patients who have received brucella treatment. In addition, asymptomatic individuals who are in frequent contact with animals may only have test positivity, which is revealed by serological screening. This leads to confusion in the diagnosis of infections that develop for different reasons in endemic areas. (9). In severe infections, serology may result in false negatives for reasons such as prozone and blocking antibodies. For these reasons, serological tests are insufficient for diagnosis. Therefore, it is important to use clinical and laboratory parameters together. (10,11)

Many publications show that fever is the most common symptom in patients with bacteremia. (3,4,10,14-16). However, due to the large number of patients in developing countries, antibiotics are started without a differential diagnosis in patients with fever, and because the disease is partially suppressed, the diagnosis is delayed and becomes chronic. (4,17-18). The detection of bacteria in the blood is much higher in patients with acute severe(intense) clinics such as fever, chills, and tremble. (19). In this study, the number of patients with fever and chills as symptoms at presentation was higher in patients with bacteremia than in patients without bacteremia (p=0.002 and p < 0.001, respectively).

There is no specific age group for the transmission of the disease. All individuals who come into contact with the disease are at risk for transmission. Since our study was performed on adult individuals, the mean age was 45.40±17.45.

A previous brucellosis disease does not give immunity to the patient, so brucella bacteria can be transmitted again in contact with the source of infection. Disruptions in treatment, such as irregular drug use, can lead to relapse. (12).

The main mode of transmission of brucellosis is the consumption of contaminated food. Consumption of

milk and dairy products prepared without boiling is the most important source of infection in the community. Butter, cream, ice cream, and fresh cheese prepared from contaminated milk are important dairy products that play a role in the transmission of infection. Infection transmission is reduced by fermented foods and boiling milk. Another mode of transmission is the direct contact of the genital secretions, milk, placentas, fetal fluids, and membranes of infected animals with damaged skin or mucous membranes, or by inhalation of infected dust spread into the environment. Rarely, there are reports of transmission through blood and organ transfusion, laboratory contact, breast milk, or sexual contact (10). Consumption of milk and dairy products was the most common mode of transmission in our study. There was no significant difference between the two groups in terms of transmission route.

The musculoskeletal system is most commonly affected by brucellosis and causes complications such as spondylitis, sacroiliitis, arthritis, tenosynovitis, and osteomyelitis (4-5,15,20). Musculoskeletal system involvement is detected by imaging methods. With a prevalence ranging from 25% to 76%, osteoarticular involvement is the most common complication of brucellosis (4). In our study, 63.4% of 123 patients had osteoarticular involvement and it was statistically higher in patients without bacteremia (p=0.023).

In patients with brucellosis, hepatosplenomegaly can be detected with a mild nonspecific elevation of 20-40% liver enzyme levels (4,21). Although hepatitis is common, it is usually subclinical and jaundice is rare (5,15,21-22). In our study, AST ($p < 0.001$) and ALT (p=0.039) elevations in bacteremic patients showed a statistically significant difference compared to those in non-bacteremic.

Anemia is one of the most common laboratory findings. Leukopenia or leukocytosis, thrombocytopenia, and pancytopenia are among other pathological laboratory findings (4,15,23). In our study, leukopenia was found in 17.9% of the patients, and WBC was between 4,000-10,000/mm³ in 75.6% of the patients. The presence of AST ($p < 0.001$), ALT (p=0.039) elevation, and leukopenia (p=0.013) in bacteremic patients showed a statistically significant difference compared to non-bacteremic patients.

CONCLUSION

Its morbidity is increasing due to the problems experienced in diagnosing and treating brucellosis. For this reason, laboratory tests required as a result of a good physical examination accompanied by a detailed anamnesis will be effective in the diagnosis. In our study, fever, and chills were frequently observed in bacteremic brucellosis patients, while osteoarthritis was more common in non-bacteremic patients. Low serum WBC and high AST can be used as potential laboratory markers for the diagnosis of brucellosis in bacteremic patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Ankara City Hospital No: 1 Clinical Researches Ethics Committee (Date: 29/06/2022, Decision no: E1/2751/2022).

Informed Consent: Not applicable.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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