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Clinical, Laboratory, and Epidemiological Characteristics of Patients Diagnosed with Brucellosis: A Comprehensive Analysis

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Abstract

Introduction: This study aims to evaluate the demographic characteristics, clinical manifestations, laboratory findings, radiological features, and the relationship between brucella capture titers and blood culture positivity in patients followed up due to brucellosis.

Methods: The medical records of 214 patients diagnosed with brucellosis, who were followed up at the infectious diseases clinic and/or outpatient clinic between January 2017 and December 2018, were retrospectively reviewed. Demographic and clinical characteristics of 118 included patients were recorded. Brucella capture tests and blood cultures were processed at bacteriology department of Dicle University Hospital Laboratory.

Results: The mean age of the patients was 39.54±17.123 years. Fifty percent of the patients were male and 58.5% of the patients resided in rural areas. The most common complaints at presentation were fever (89%) and bone-joint pain (73.7%). The most frequent physical examination findings were fever (89%) and tenderness in bones and joints (73.7%). Elevated erythrocyte sedimentation rate was observed in 29.6% of patients, while elevated c-reactive protein levels were seen in 55.9% of the patients. The two most common hematological findings at the time of diagnosis were anemia with 45.8% and lymphomonocytosis with 26.3%. A statistically significant disparity was observed in the incidence of complications among patients displaying hematological manifestations, including anemia, leukopenia, and thrombocytopenia, associated with brucellosis ($p<0.05$). The most commonly encountered organ involvements were sacroiliitis, with a prevalence of 31.4%, and splenomegaly, noted in 25.4% of cases. Among the patient cohort, disease reporting was documented in 59.3% of instances. The reporting rate was notably higher at the infectious diseases clinic, accounting for 64.7% of cases, whereas non-infectious clinics exhibited a lower reporting rate of 25%. Blood cultures were taken from 56 of 118 patients followed up due to brucellosis and growth was detected in 30 of them. All of the microorganisms grown were determined to be B. Melitensis. Notably, 62.5% of patients with a brucella capture titer ≥1/ 1280 and 31.25% of those with titers <1/ 1280 exhibited growth in blood cultures. There was a statistically significant correlation between the elevation of brucella capture titers among patients, ranging from 1/320 to 1/5120, and an increased likelihood of detecting brucella bacteria through blood culture ($p<0.05$).

Conclusion: This study revealed a correlation between higher brucella capture titers and blood culture positivity. In addition, markers such as anemia, leukopenia, and thrombocytopenia were associated with an increased risk of complications, emphasizing their importance as prognostic indicators.

Key Words: brucella capture, blood culture, complication.

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Bruselloz Tanısı Alan Hastaların Klinik, Laboratuvar ve Epidemiyolojik Özellikleri: Kapsamlı Bir Analiz

Öz

Giriş: Bu çalışmada bruselloz nedeniyle takip edilen hastaların demografik özellikleri, klinik, laboratuvar, radyolojik bulguları ve brusella capture titresi ile kan kültür pozitifliği arasındaki ilişkinin de değerlendirilmesi amaçlanmıştır.

Metod: Ocak 2017-aralık 2018 tarihleri arasında enfeksiyon hastalıkları klinik ve/veya polikliniklerinde izlenen bruselloz tanısı alan 214 hastanın tıbbi kayıtları retrospektif olarak incelendi. Dahil edilen 118 hastanın demografik ve klinik özellikleri kaydedildi. Brucella capture testleri ve kan kültürleri Dicle Üniversite Hastanesi Laboratuvarı bakteriyoloji bölümünde değerlendirildi.

Bulgular: Hastaların yaş ortalaması 39.54±17.123 olarak saptandı. Hastaların %50'si erkek olup, %58,5'i kırsal alanda yaşıyordu. Başvuru anında en sık iki şikâyetin %89 ile ateş, %73,7 ile kemik-eklem ağrısı olduğu izlendi. Hastalarının tanı anındaki en sık iki fizik muayene bulgusu %89 ile ateş %73,7 ile kemik ve eklemlerde hassasiyet olarak izlendi. Eritrosit sedimentasyon hızı yüksekliği hastaların %29,6'sında, c-reaktif protein yüksekliği ise hastaların %55,9'unda izlendi. Tanı anında en sık iki hematolojik bulgu %45,8 ile anemi %26,3 ile lenfomonositoz olarak izlendi. Bruselloza bağlı anemi, lökopeni ve trombositopeni dahil olmak üzere hematolojik belirtiler gösteren hastalar arasında komplikasyonların insidansında istatistiksel olarak anlamlı bir farklılık gözlendi ($p<0.05$). En sık görülen iki tutulum %31,4 ile sakroileit, %25,4 ile splenomegali olarak izlendi. Bruselloz nedeniyle takipli 118 hastanın 56'sından kan kültürü alındığı ve bunlardan 30'unda üreme olduğu saptandı. Üreyen mikroorganizmaların tamamının B. Melitensis olduğu tespit edildi. Brusella capture titresi ≥1280 olan hastaların %62,5'inde; <1280 olan hastaların %31,25'inde kan kültüründe üreme olduğu izlenmiştir. Hastaların brusella capture titresi yükseldikçe (1/320 den 1/5120'ye doğru gidildikçe) kan kültüründe brusella bakterisini izole etme oranında istatiksel olarak anlamlı bir fark saptandı ($p<0.05$).

Sonuç: Bu çalışma, yüksek brusella capture titreleri ile kan kültürü pozitifliği arasında bir korelasyon ortaya koydu. Ek olarak, anemi, lökopeni ve trombositopeni gibi belirteçler, komplikasyon riskinin artmasıyla ilişkilendirildi ve bunların prognostik göstergeler olarak önemi vurgulandı.

Anahtar kelimeler: brusella capture, kan kültürü, komplikasyon.

INTRODUCTION

Brucellosis, a significant zoonotic disease with global public health importance, while not highly fatal, can impact a substantial number of individuals annually and lead to workforce productivity loss. Moreover, the disease can result in considerable economic losses due to factors such as abortion, infertility, premature birth, animal deaths, and reduced milk production in animals. The spread of brucellosis to specific regions is closely associated with local livestock activities. It is observed in various parts of the world, including the Mediterranean Basin, Arabian and Indian Peninsulas, Mexico, Central and South America[1,2]. In Turkey, the highest incidence is reported in the Southeastern Anatolia, Eastern Anatolia, and Central Anatolia regions[3].

Brucellosis is a zoonotic disease characterized by a fluctuating fever pattern with chills, sweating, and musculoskeletal pain. It can be transmitted to humans through direct contact with infected animals, consumption of unpasteurized dairy products, or inhalation of contaminated droplets. The disease can affect multiple organs and systems within the human body, presenting with a range of symptoms. While the onset of brucellosis can be silent or acute, symptoms typically emerge 2-4 weeks after inoculation. Depending on the duration of symptoms, brucellosis is classified as acute (<8 weeks), subacute (8-52 weeks), or chronic (>1 year). The disease can also manifest as focal or localized organ involvement[4,5].

Definitive diagnosis of brucellosis is established through culture. Depending on complications, clinical course, and patient condition, suitable materials for culture include blood, urine, joint fluid, cerebrospinal fluid, lymph node aspirate, abscess material, other body fluids, and tissues. The yield of blood culture ranges between 15% and 70% depending on the method used and the incubation period. Blood culture exhibits good

sensitivity for B. melitensis, while sensitivity for B. abortus and B. suis is relatively lower. Due to their facultative intracellular nature, Brucella species have higher culture yield in bone marrow cultures compared to blood cultures[1,4-6].

Brucellosis treatment entails various regimens, although optimal duration and regimen for relapses, chronic, and complicated cases remain uncertain. The treatment consists of antibiotic therapy, rest, symptomatic and supportive care. Bed rest is advised until fever subsides. Acutely severe brucellosis cases should be treated in a hospital setting[3,7].

Given the non-specific nature of symptoms and their resemblance to other diseases, the patient's history holds paramount importance in brucellosis diagnosis. This study aims to examine demographic and clinical characteristics, laboratory and radiological findings, treatment combinations, and the relationship between complicated cases and relevant parameters in patients with brucellosis. Additionally, the study aims to assess the correlation between Brucella capture titers and positive blood cultures.

METHODS

This retrospective observational study was conducted between January 2018 and December 2019, focusing on 214 patients diagnosed with brucellosis who were monitored at the department of ınfectious diseases inpatient and/or outpatient clinic. Patients who were not continuing their treatment at Dicle University Medical Faculty Hospital and those under the age of 18 were excluded from the study. The study encompassed variables such as age, gender, medical history of chronic diseases, place of residence, fever, arthralgia, night sweats, nausea-vomiting, hemoglobin level, white blood cell count, presence of lymphomonocytosis, platelet count, Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), brucella capture titer, presence of growth in blood culture, treatment regimens employed, relapses, complications (hepatomegaly, splenomegaly, epididymo-orchitis, sacroiliitis, spondylodiscitis, sepsis, neurobrucellosis, bone marrow suppression), whether consultation was provided, and the pregnancy outcomes of individuals who contracted brucellosis during pregnancy.

Patient information for those who were hospitalized and followed up at the clinic was extracted by scanning patient files from the hospital's computer operating system and clinical file archive. Data for patients followed up as outpatients were obtained by examining outpatient clinic follow-up forms and laboratory test results recorded in the hospital's computer operating system. Abdominal ultrasonography was performed on patients with hepatomegaly and/or elevated liver enzymes and/or pancytopenia detected during physical examination. Direct X-rays and contrast-enhanced magnetic resonance imaging (MRI) reports were reviewed for patients as indicated. For patients with detected murmurs during cardiac examination or prolonged fever, echocardiography reports were assessed for infective endocarditis. Contrast-enhanced brain Magnetic Resonance Imaging reports were reviewed for patients with prolonged headache, persistent nausea-vomiting, or central nervous system symptoms, and the results of lumbar puncture with cerebrospinal fluid sampling were examined.

The data were analyzed using the SPSS version 24 statistical software package. Categorical measurements were summarized as numbers and percentages, while continuous measurements were summarized as means and standard deviations (with minimum-maximum values where necessary). The Chi-square test was applied for comparing non-numerical variables. Non-parametric tests were utilized

for comparing binary variables with numerical data. The obtained results were evaluated at a significance level of 95% ($p<0.05$).

Ethical approval for the study was obtained from the Ethics Committee of Dicle University Medical Faculty under protocol number 289 on February 6, 2020.

RESULTS

A total of 118 patients were included in the study, of which 59 (50%) were male. The patients' ages ranged from 17 to 84 years, with a mean age of 39.54 ± 17.1 years. Among the patients, 69 (58.5%) resided in rural areas, and 23 (19.5%) had a history of chronic diseases. It was determined that 31 (26.2%) of the patients had relapsing cases at their initial presentation.

Table 1 displays the demographic characteristics of the 31 patients who were assessed as relapse-brucellosis cases at the time of hospital admission. While some numerical differences were observed in the results, no statistically significant differences were found.

Table I: Demographic Characteristics of Patients Presenting with Relapsed Brucellosis

	Recurrence Yes (n)	Recurrence No (n)	p
Gender			
Male	12	47	0.134
Female	19	40	
The place of residence			
Town center	14	35	0.396
Rural al	17	52	
Chronic disease			
Yes	8	15	0.467
No	23	72	

The most common complaint at the time of presentation was fever, accounting for 89% of cases, followed by bone-joint pain at 73.7%. The frequencies of complaints are shown in Table 2.

Table II: Complaints of Patients at the Time of Application to the Hospital

Complaints n=118	n (%)
Fever	105 (89)
Bone-joint pain	87(73.7)
Night sweating	69(58.5)
Nausea-vomiting	38 (32.2)
Headache	2 (1.7)

The most common physical examination finding at the time of diagnosis was fever (89%), followed by tenderness and/or limited movement in bones and joints (87%). The frequencies of physical examination findings are presented in Table 3.

Table III: Physical Examination Findings of the Patients at the Time of Diagnosis

Physical examination finding n=118	n (%)
Fever	105 (89)
Tenderness in Bones and Joints	87 (73.7)
Splenomegaly	30 (25.4)
Hepatomegaly	29 (24.6)
Murmur in the Heart	1 (0.8)

Among the hematological findings, anemia was the most commonly observed, affecting 54.8% of the patients. This was followed by lymphomonocytosis (26.3%), thrombocytopenia (16.1%), leukocytosis (12.7%), leukopenia (10.2%), and thrombocytosis (0.8%).

Blood cultures were taken from 56 of 118 patients followed up due to brucellosis, and growth was detected in 30 of them. All of the microorganisms grown were determined to be

B. Melitensis. Surprisingly, B. melitensis was grown in the pleural culture of a 44-year-old male patient who was followed up for empyema. Additionally, among patients with brucella capture titers≥1/1280, growth was observed in blood culture for 62.5%, while among patients with titers below 1/1280, growth was observed in 31.25%. Furthermore, a statistically significant correlation was found between increasing brucella capture titers (from 1/320 to 1/5120) and the isolation rate of brucella bacteria in blood culture ($p<0.05$) (Table 4).

Table IV: Brucella-Capture Titers and Positivity in Culture of Patients

	Brusella-Capture	**N**
Pozitif brucella culture	320	3
	640	2
	1280	6
	2560	6
	5120	13
	Total	30
Negative brucella culture	320	5
	640	6
	1280	4
	2560	8
	5120	3
	Total	26
	Brucella-capture ≥1280 n(%)	**Brucella-capture <1280 n(%)**
Pozitif brucella culture	25 (62.5)	5 (31.25)
Negative brucella culture	15 (37.5)	11 (68.75)

Sacroiliitis was the most common complication observed (31.4%), followed by splenomegaly (25.6%). The frequencies of complications are presented in Table 5.

Table V: Complications in Patients Follow-up for Brucellosis

Complications	**n (%)**
Sacroiliitis	37 (31.4)
Splenomegaly	30 (25.4)
Hepatomegaly	29 (24.6)
Bone marrow suppression	21 (17.7)
Spondylodiscitis	17 (14,4)
Epididymoorchitis (59 male patients)	7 (23.6)
Osteomyelitis	7 (5.9)
Sepsis	7 (5.9)
Neurobrucellosis	2 (1.7)
Endocarditis	1 (0.8)
Pleural effusion	1 (0.8)

An examination of the relationship between patients' demographic and hematological characteristics and the development of complications (Table 6) revealed a statistically significant correlation between the presence of anemia, leukopenia, thrombocytopenia, and the occurrence of complications ($p<0.05$).

Table VI: Demographic and Hematological Findings of Patients with Complications

	Complication yes (n= sayı)	**Complication no (n= sayı)**	**p**
Gender			
Male	42	17	0.840
Female	41	18	
The place of residence			
Town center	30	19	0.068
Rural	53	16	
Chronic disease			
Yes	19	4	0.151
No	64	31	
Anemia			
Yes	44	10	**0.015**
No	39	25	
leukopenia			
Yes	12	0	**0.018**
No	71	35	
Lymphmonocytosis			
Yes	22	9	0.929
No	61	26	
Thrombocytopenia			
Yes	19	0	**0.002**
No	64	35	

Table 7 outlines the treatment regimens administered to patients followed up for brucellosis at our hospital. The most commonly used combination was doxycycline + rifampicin (54.2%), followed by rifampicin + trimethoprim/sulfamethoxazole (TMP-SMX) (8.5%) and doxycycline + rifampicin + TMP-SMX. Treatment regimens were chosen based on factors such as local involvement, age, drug allergies, interactions with medications taken for comorbid conditions, and pregnancy status.

Table VII: Antibiotherapy Combinations of Patients Follow-up for Brucellosis

Treatment	Count (n)	Frequency (%)
Tetradox+Rifampicin	64	54.2
Rifampicin+ TMP-SMX	10	8.5
Tetradox+Rifampicin+TMP-SMX	10	8.5
Tetradox+Streptomycin	9	7.6
Tetradox+Rifampicin+Streptomycin	6	5.1
Tetradox+TMP-SMX	2	1.7
Rifampicin+Tetradox+Gentamicin	4	3.4
Tetradox+Rifampicin+Ceftriaxone	3	2.5
Tetradox+Rifampicin+Ciprofloxacin	3	2.5
Tetradox+TMP-SMX+Streptomycin	2	1.7
Tetradox+Ceftriaxone+TMP-SMX	1	0.8
Ciprofloxacin+TMP-SMX+Tetradox	1	0.8
Ceftriaxone + Rifampicin	1	0.8
Streptomycin + Rifampicin	1	0.8
Rifampicin+TMP+SMX+Ceftriaxone	1	0.8
Total	**118**	**100.0**

In consideration of the diverse organ systems affected by brucellosis, variations in the clinical departments attended by patients are plausible. The investigation revealed that the majority of participants (102 patients, 86.4%) sought medical attention at the infectious diseases unit during their initial visit. Eight patients sought care at the internal medicine department, five patients at the physical therapy-rehabilitation department, while one patient each presented to the urology, obstetrics, and psychiatry clinics.

As per the health regulations of our nation, mandatory reporting of brucellosis cases is enforced. In our research, 70 individuals (59.3% of the total) were subjected to reporting. Among them, 66 cases originated from the infectious diseases clinics (66/102, 64.7%), while the remaining four cases were reported from non-infectious diseases departments (4/16, 25%).

DISCUSSION

Brucellosis, caused by various species of the Brucella genus, remains a significant public health concern in many parts of the world. In this retrospective observational study, we aimed to elucidate several aspects of brucellosis, including clinical presentations, diagnostic approaches, treatment regimens, and associated complications. This study also aimed to reveal the relationship between brucella capture titers and blood culture positivity.

Although brucellosis is more common in males due to occupational exposure in regions where brucellosis is not endemic; there is no gender difference in regions where the disease is endemic[10,11]. No significant difference was observed in terms of gender in studies conducted in our country[12]. In this study, 50% of the patients were male, which was compatible with the gender data in other studies.

According to the literature, the most common complaints of brucellosis were reported as fever (46.7-95%), fatigue (18.2-97.5%), sweating (8.6-91%), night sweats (18.9-81%), joint pain (20.4-85.6%) and headache (7-64%)[3,8,13,15-26]. In this study, fever was found in 89%, bone-joint pain in 73.7%, night sweats in 58.5%, nausea-

vomiting in 32.2%, and headache in 1.7% of the patients.

In the literature, various ranges of percentages have been reported for specific physical examination findings associated with brucellosis, including fever (28.8-91.3%), arthritis (5.7-85%), hepatomegaly (5.3-55%), splenomegaly (9.6-44.1%), and murmur (2-21.1%)[8,11,13-17,19-21,24-27]. In this study, physical examination findings included fever in 89% of the patients, tenderness in bones and joints in 73.7%, splenomegaly in 25.4%, hepatomegaly in 24.6%, and heart murmur in 0.8%.

In the studies under examination, the growth rate in blood cultures ranged from 7% to 72.5% [8,9,18,27,29,30]. In the present study, the rate of positive growth in blood culture was observed to be 53.5%. Among patients with brucella capture titers ≥ 1/1280, growth was observed in blood culture for 62.5%. Furthermore, as the Brucella capture titer increased (ranging from 1/320 to 1/5120), a statistically significant difference emerged in the rate of successful isolation of Brucella bacteria from blood cultures (p=0.014). Patients with higher Brucella capture titers showed a heightened likelihood of successful bacterial isolation in blood cultures. This observation underscores the potential utility of brucella capture titers as a predictive tool for positive blood culture results. While this study makes a significant contribution to the literature by revealing the relationship between high brucella capture titer and bacteremia, more studies are needed to reveal its effect on clinical outcome.

Complications associated with brucellosis, as documented in the literature, encompass osteoarticular complications (17.3%-69%), hematological complications (1.7%-46.6%), hepatic complications (2.7%-33.3%), genitourinary complications (1%-20%), neurological complications (10%), cutaneous complications (2%-6%), and infrequently occurring cardiac and respiratory complications[5,7,13-17,26-36].

In the current study, the prevalence of complications was as follows: 31.7% of patients exhibited sacroiliitis, 23.6% had genitourinary complications, 17.7% experienced hematological complications, 14.4% presented with spondylodiscitis, 5.9% displayed osteomyelitis, and 1.7% had neurological complications. Interestingly, no cutaneous complications were identified, while cardiac complications (pleural effusion) were observed in 0.8% of patients. Furthermore, it is noteworthy that a 56-year-old female patient succumbed to brucella-associated sepsis.

Demographic factors such as gender, place of residence, and history of chronic disease, along with hematological characteristics including anemia, leukopenia, thrombocytopenia, and lymphomonocytosis, were examined in patients who experienced complications. The significant relationship between the presence of hematological abnormalities (anemia, leukopenia, thrombocytopenia) and the occurrence of complications suggests a potential association between disease severity and the development of complications. Based on these findings, it may be advisable to closely monitor patients exhibiting anemia, leukopenia, and thrombocytopenia.

The primary limitations of this study are its single-center nature, its inclusion of exclusively adult patients, and its retrospective design.

In conclusion, this study contributes to the comprehensive understanding of brucellosis, encompassing various aspects of its clinical presentation, diagnosis, and treatment. The observations pertaining to clinical manifestations, hematological abnormalities, microbiological aspects, and treatment regimens enhance our knowledge of this complex zoonotic disease.

Due to the diverse range of symptoms and presentations, brucellosis should be considered in the differential diagnosis of all patients exhibiting nonspecific signs of infection. As patients frequently seek initial care from clinics outside the field of infectious diseases, it becomes crucial to ensure that all physicians possess current and comprehensive knowledge of brucellosis. This can be achieved through regular training sessions that establish standardized diagnostic and treatment protocols. Further research is warranted to elucidate the underlying mechanisms of complications, ultimately contributing to improved management strategies and patient outcomes.

Ethics Committee Approval: Ethical approval for the study was obtained from the Ethics Committee of Dicle University Medical Faculty under protocol number 289 on February 6, 2020.

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