



Childhood Brucellosis: Analysis of 77 Cases

Çocukluk Çağı Brusellozu: 77 Olgunun İrdelenmesi

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Abstract

Objective: Brucellosis, a prevalent zoonotic disease endemic in Türkiye, poses a significant public health problem. Children account for 20-25% of brucellosis cases in our country. This study aims to investigate the epidemiological characteristics, clinical symptoms, laboratory findings, and treatment regimens among pediatric brucellosis patients.

Material and Methods: Pediatric brucellosis patients admitted to our hospital between January 2022 and December 2022 were included in this study. Patients were retrospectively examined for clinical, laboratory, and epidemiological characteristics. Data from both outpatient and inpatient settings were compared.

Results: Among the 77 children diagnosed with brucellosis, 43 (56%) were boys with a median age of nine years, and 34 (44%) were girls with a median age of 10 years. Brucellosis was most common in September and predominantly occurred during autumn. Most of the cases had a history of consuming raw milk or dairy products, with a positive family history noted in 49 (64%) cases. The most prevalent symptoms included fever (100%) and joint pain (62%). Common laboratory findings included anemia (14%) and leukopenia (18%), with leukocytosis observed in four patients. Percent forty-eight of patients required hospitalization and treatment. Gender and age distributions were similar between inpatients and outpatients. The standard tube agglutination (Wright) test values were significantly higher in inpatients compared to outpatients ($p < 0.05$). No significant differences were found in other evaluated laboratory values between outpatients and inpatients.

Conclusion: Hematopoietic system involvement is frequent in pediatric brucellosis. In endemic regions like ours, brucellosis should be considered in febrile cases accompanied by rheumatological symptoms. Moreover, the standard tube agglutination (Wright) test, which aids in diagnosing brucellosis, can help predict the need for hospitalization in patients.

Keywords: Fever, laboratory findings, pediatric brucellosis, standard tube agglutination

Öz

Giriş: Bruselloz yaygın olarak görülen zoonotik bir hastalık olup Türkiye'de endemik olarak görülmekte ve ciddi bir halk sağlığı sorunu oluşturmaktadır. Ülkemizde çocuklar, bruselloz vakalarının %20-25'ini oluşturmaktadır. Bu çalışmada, pediatrik bruselloz hastalarının epidemiyolojik özellikleri, klinik belirtileri, laboratuvar bulguları ve tedavi kombinasyonları üzerine bir inceleme yapılmıştır.

Gereç ve Yöntemler: Bu çalışmaya Ocak 2022-Aralık 2022 tarihleri arasında hastanemize başvuran pediatrik bruselloz hastaları dahil edilmiştir. Hastalar klinik, laboratuvar ve epidemiyolojik özellikleri açısından retrospektif olarak incelenmiştir. Ayrıca, ayaktan ve yatarak tedavi edilen hastaların verileri karşılaştırılmıştır.

Bulgular: Bruselloz tanısı konulan 77 çocuktan 43 (%56)'ü erkek, yaş medyan dokuz, 34 (%44)'ü kız, yaş medyan değeri 10 idi. Bruselloz tanısı en fazla eylül ayında; mevsim olarak en fazla sonbaharda konulmuştur. Olguların çoğunda çiğ süt veya süt ürünü tüketme öyküsü olup 49 (%64) olguda aile öyküsü pozitif olarak bulunmuştur. En sık görülen semptomlar ateş (%100) ve eklem ağrısı (%62) idi. Hastalarda en sık görülen laboratuvar bulgusu anemi (%14) ve lökopeni (%18) idi; dört hastada lökositöz gözlemlendi. Hastaların %48'i yatırılarak tedavi edildi. Yatan ve ayaktan takip edilen hastaların cinsiyet ve yaş dağılımları benzer bulundu. Yatan hastaların standart tüp aglütinasyon (Wright) test değeri ayaktan hastalara göre anlamlı olarak daha yüksek bulundu ($p < 0.05$). Ayaktan ve yatan hastalar arasında değerlendirilen diğer laboratuvar değerleri açısından ise fark bulunmadı.

Sonuç: Çocukluk çağı brusellozunda hematopoetik sistem tutulumu sıkça görülebilir. Bölgemiz gibi brusellozun endemik olarak görüldüğü yerlerde, romatolojik yakınmaların eşlik ettiği ateşli hastalıkların varlığında bruselloz düşünülmelidir. Ayrıca bruselloz tanısı koymada yol gösterici olan standart tüp aglütinasyon (Wright) testi, hasta yatış öngörüsü sağlayabilmektedir.

Anahtar Kelimeler: Ateş, laboratuvar bulguları, pediatrik bruselloz, standart tüp aglütinasyon

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Introduction

Brucellosis is a significant public health concern affecting both animals and humans in many countries worldwide (1). It is caused by gram-negative, facultative intracellular bacteria of the *Brucella* genus, capable of infecting various organs and soft tissues (2). In Türkiye, it is prevalent in the central, eastern, and southeastern regions, affecting not only adults but also children (3). Approximately 20-30% of cases are diagnosed during childhood (4-6). This zoonotic disease, which classically presents as an influenza-like syndrome, remains endemic in most developing countries, especially in areas of intensive agriculture, and transmission is usually through the consumption of unpasteurized dairy products (7). Unlike adults, nearly all pediatric cases are associated with the consumption of unpasteurized milk or dairy products (3).

Clinical symptoms of brucellosis are nonspecific and include fever, night sweats, arthralgia, fatigue, anorexia, and back pain. Therefore, it can sometimes be mistaken for malignancies, collagen vascular diseases, tuberculosis, malaria, rheumatic fever, or leishmaniasis (8,9). This infectious disease is a common cause of fever of unknown origin among children, especially in endemic countries (10).

While the gold standard for diagnosing brucellosis involves isolating the microorganism, the most commonly used diagnostic method is the standard/Wright tube agglutination test, with titers of 1/160 or higher considered positive (11). Laboratory findings such as leukocytosis/leukopenia, relative lymphocytopenia, anemia, thrombocytopenia, elevated C-reactive protein (CRP), and high erythrocyte sedimentation rate (ESR) can be observed but are not specific for diagnosis (12).

Treatment recommendations by the World Health Organization (WHO) have remained unchanged since 1986, advocating for optimal combinations such as doxycycline + rifampicin or streptomycin. However, cases where WHO indications are not followed have been reported in the literature (1). Additionally, the recommended treatments are not always completely effective, with recurrence rates ranging from 5% to 15% (13).

In this study, we aimed to investigate the epidemiological characteristics, clinical symptoms, laboratory findings, and treatment regimens of pediatric brucellosis cases in our endemic region.

Materials and Methods

In this retrospective observational study, we analyzed the epidemiological characteristics, laboratory and clinical findings, and treatment regimens of childhood brucellosis cases between January 2022 and December 2022.

Brucellosis diagnosis was based on the presence of symptoms such as arthralgia, fatigue, and night sweats, along with a

positive Rose Bengal test and *Brucella* tube agglutination test titers of 1:160 and/or Coombs test titers of 1:80, or isolation of *Brucella* species from body fluid samples such as blood (14-16). Indications for hospitalization included severe infection manifestations such as endocarditis, meningitis, osteoarticular involvement, neurobrucellosis, bacteremia, and systemic deterioration requiring intravenous antibiotics (17).

Demographic characteristics, clinical signs, complete blood count, CRP, ESR, liver enzyme levels aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), results of Rose Bengal, standard tube agglutination (STA), and Coombs agglutination tests, as well as treatment regimens, were obtained from hospital electronic records. Data from outpatient and inpatient brucellosis cases were compared.

The threshold for anemia was defined as follows: 10.5-14 g/dL; for ages 1-6 years, 11.5-15.5 g/dL; for ages 6-12 years, 12-16 g/dL; for boys aged 12-18 years, and 13-16 g/dL; for girls aged 12-18 years. The normal ranges for leukocyte (white blood cell) counts were considered as follows: For ages 1-4 years, $6-17.5 \times 10^9/L$; for ages 4-8 years, $5.5-15.5 \times 10^9/L$; for ages 8-13 years, $4.5-14.5 \times 10^9/L$; and for ages 13-18 years, $4-10 \times 10^9/L$. The normal range for platelet counts was considered to be 150.000-400.000/mL. ALT levels >35 IU/L, AST levels >40 IU/L, GGT levels >55 IU/L, CRP levels >5 mg/L, and ESR >20 mm/h were regarded as elevated.

The study was approved by the Van Research and Training Hospital Clinical Research Ethics Committee on November 15, 2023, with decision number 2023/24-04.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 20 (IBM, United States of America). Data were analyzed using descriptive statistics [mean, median, standard deviation (SD), percentage]. The Shapiro-Wilk test was used to assess the normality of the data distribution. Normally distributed data were expressed as "mean \pm standard deviation", while non-normally distributed data were expressed as "median (25th percentile - 75th percentile)".

Results

Seventy-seven pediatric patients diagnosed with brucellosis between January 2022 and December 2022 at our hospital were included in this study. Of the patients, 43 (56%) were boys and 34 (44%) were girls. The mean age of the patients was 9.5 ± 4.3 years, with a median age of 10 years (minimum 1 year; maximum 17 years). The highest number of cases was observed in September (19.4%). Seasonally, most diagnoses were made in the autumn (Figure 1). A history of consuming raw milk or dairy products was present in most cases (97%), with two cases (3%) having a history of contact with animals, and 49 cases (64%) having a positive family history.

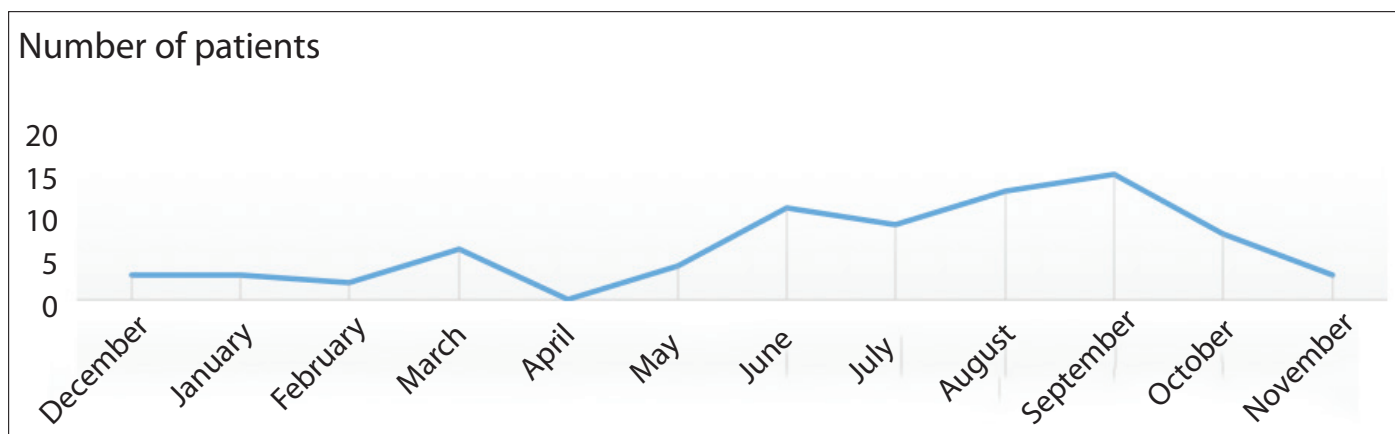


Figure 1. Number of patients by months.

The most common symptoms were fever (100%), joint pain (62%), diarrhea (17%), and muscle pain (13%) (Table 1).

Three patients developed splenomegaly, one developed arthritis, one developed endocarditis, and one developed sacroiliitis. The patient with endocarditis also had splenomegaly and *Brucella* spp. growth was isolated in the blood culture. The tube agglutination test value for this patient was 1/1280. Due to the risk of embolism and the potential need for cardiac surgery, the patient was referred to a center with an intensive care unit.

In our study, 25 patients (32%) had at least one episode of hematologic involvement, and 1 patient (1%) had pancytopenia. The most common laboratory findings in children were leukopenia (18%) and anemia (14%), with four patients exhibiting leukocytosis. Other laboratory values for the patients are shown in Table 2.

Regarding the tube agglutination test results, 1 patient (1%) was negative (this patient had a positive blood culture), 14 patients (19%) had a titer of 1/160, 18 patients (23%) had a titer of 1/320, 30 patients (39%) had a titer of 1/640, 8 patients

Table 2. Laboratory findings of brucellosis cases

Laboratory Findings	Number (%)
Hemoglobin= g/dL	Anemia: 11 (14) Normal: 66 (86)
Leukocytes	Leukopenia: 14 (18) Normal: 59 (77) Leukocytosis: 4 (5)
Platelets	Thrombocytopenia: 5 (6) Normal: 65 (85) Thrombocytosis: 7 (9)
C-reactive protein (not analyzed in seven cases)	Normal: 43 (65) High: 27 (35)
Erythrocyte sedimentation rate (not analyzed in 30 cases)	Normal: 22 (29) High: 25 (32)
ALT	Normal: 48 (62) High: 29 (38)
AST	Normal: 50 (63) High: 27 (27)
GGT* (not analyzed in five cases)	Normal: 63 (87.5) High: 9 (12)

GGT: Gamma glutamyl transferase.

Table 1. Patients' symptoms at presentation

Symptoms at Presentation	Number (%)
Fever	77 (100)
Arthralgia	48 (62)
Diarrhea	13 (17)
Muscle pain	10 (13)
Fatigue	7 (9)
Lower back pain	5 (6)
Abdominal pain	3 (4)
Hip pain	3 (4)
Weight loss	2 (3)
Nausea/vomiting	1 (1)
Rash	1 (1)

(10%) had a titer of 1/1280, and 6 patients (8%) had a titer of 1/2560 or higher. *Brucella* spp. growth was identified in the blood culture of four hospitalized patients.

Forty-three patients (56%) were treated with a combination of two antimicrobial drugs, and 34 patients (44%) were treated with a combination of three antimicrobial drugs. The most commonly used treatment combination was rifampicin and trimethoprim-sulfamethoxazole (18%). The next most commonly used treatment combination included rifampicin, trimethoprim-sulfamethoxazole, and gentamicin for the first five days.

Of the 77 patients included in the study, 37 were hospitalized. Detailed demographic data and tube agglutination test values for outpatient and inpatient groups are provided in Table 3. Gender (p= 0.76) and age distribution (p= 0.41) were comparable between inpatient and outpatient groups.

Table 3. Demographic and clinical data of outpatient and inpatient brucellosis cases

		Inpatient (n= 37)		Outpatient (n= 40)		p
		n	(%)	n	(%)	
Gender	Female	17	(46)	17	(43)	0.760
	Male	20	(54)	23	(47)	
Age (years)		9.4 ± 4.1		9.6 ± 4.5		0.413
Brucella tube agglutination	1/160	3	(8.1)	11	(27.5)	<0.05
	1/320	7	(19)	11	(27.5)	
	1/640	15	(40.5)	15	(37.5)	
	1/1280	6	(16.2)	2	(5)	
	1/2560	5	(13.5)	1	(2.5)	

Table 4. Laboratory values of outpatients and inpatients with pediatric brucellosis

	Inpatient		Outpatient		p
	n	Median Value (minimum-maximum)	n	Median Value (minimum-maximum)	
ALT (IU/L)	37	34 (20.25-55.75)	40	22.5 (17-45.75)	0.072
AST (IU/L)	37	34 (28-52)	40	31 (21.25-52.25)	0.267
Eosinophil	37	0.1 (0.01-0.21)	40	0.1 (0.05-0.14)	0.643
Monocyte	37	0.44 (0.305-0.54)	40	0.42 (0.3325-0.625)	0.541
White blood cells	37	7.29 (±2.775)	40	6.325 (4.8825-8.9675)	0.971
CRP*	35	10.2 (4.9-32.3)	35	14.02 (2.7-21.09)	0.928
ESR**	23	28 (14-37)	24	17.5 (12.25-28.75)	0.180
GGT***	36	19.04 (15.32-27.625)	36	19.73 (16.255-28.057)	0.764

*CRP: C-reactive protein.

**ESR: Erythrocyte sedimentation rate.

***GGT: Gamma glutamyl transferase.

The mean tube agglutination test value was 1/320 for outpatients and 1/640 for inpatients. The tube agglutination test values of inpatients were significantly higher than those of outpatients ($p < 0.05$) (Table 3). No significant differences were found between the laboratory values of outpatient and inpatient groups (Table 4).

Discussion

Brucellosis is one of the most common zoonoses worldwide. However, due to differences in surveillance systems among countries, the true global incidence remains unknown. In some populations, cases are believed to exceed 1/10,000 (18). The estimated global incidence of brucellosis is around 500,000 cases annually. In our country, brucellosis is a notifiable disease and is endemic, affecting many organ systems. The prevalence rate in our country is reported to be between 3-14%, with the highest rates observed in the southeastern, eastern, and central Anatolia regions (19).

In a study conducted in Iran, clinical symptoms, laboratory findings, and treatment regimens of 34 pediatric brucellosis

patients were examined. The study included one patient with negative STA and Coombs agglutination test results with a positive blood culture for *Brucella* spp. According to this study, the highest positivity rates were observed in summer and spring (10). Similarly, in our study, one patient had an STA test result of 1/80, but *Brucella* spp. was identified in the blood culture. In our study, the highest positivity rate was observed in autumn, in September. In our region, livestock farming is intensively practiced, and dairy production increases seasonally. We believe that the highest positivity rate in autumn is due to the high consumption of raw milk and dairy products among our patients.

The gender distribution of brucellosis in our study is similar to other studies, with most pediatric brucellosis cases being male (10,20-24).

The median age of the patients in our study was 10 years (minimum 1 year; maximum 17 years). A study conducted in our country on pediatric brucellosis cases also found the mean age to be 9.02 ± 3.59 years (21). Another study in Iran found that nearly half of the patients were between two and five

years old, attributing this to the higher tendency for younger children to contract the disease from dairy products (10).

Hematological changes are frequently observed in brucellosis patients. In a study by Aypak et al., 69 pediatric brucellosis cases were examined, and thrombocytopenia (15.9%) was found to be the most common hematologic finding (5). Most studies investigating pediatric brucellosis have found anemia to be the most common hematologic finding (3,21). In our study, leukopenia was the most common hematologic finding, followed by anemia. These results indicate that hematologic parameters can vary from patient to patient in brucellosis cases. The most common abnormalities in the literature include mild anemia, leukocytosis/leukopenia, and thrombocytopenia (3,5,25,26).

During any infection, such as brucellosis, elevated levels of parameters like ESR and CRP can be observed. Some studies have reported elevated ESR in 38-87% of brucellosis patients and elevated CRP in 34-81% of cases (20,21,23,24). In our study, ESR was elevated in 32% of the patients, and CRP was elevated in 35%.

The clinical symptoms of brucellosis are often nonspecific, making diagnosis challenging. As reported in adults, fever and arthralgia are the most common complaints in pediatric brucellosis (10,22,24,27-32). In our study, the most common complaints were fever (100%) and joint pain (62%).

Splenomegaly was observed in three children with brucellosis. The reported rates of organomegaly vary significantly in different studies (3,10,20-22,27,31). *Brucella* spp. affects the reticuloendothelial system, and organomegaly is often detected during physical examination. However, in our study, only a few patients had splenomegaly reported as a physical examination finding. The detection rate of organomegaly can also depend on the experience of the examiner, the quality of the physical examination, and the duration of the disease.

A study found that blood eosinophil levels were higher in hospitalized patients, suggesting that eosinophil levels might play a role in determining disease severity and the decision for hospitalization in pediatric brucellosis (33). However, in our study, there was no significant difference in blood eosinophil levels between hospitalized patients and those followed up as outpatients ($p=0.643$).

There are various treatment regimens for brucellosis. In adults, tetracyclines are recommended for treatment, but these antibiotics are generally avoided in children under eight years of age due to the risk of teeth discoloration (34). For children over eight years, the standard treatment approach is a combination of doxycycline with rifampicin, streptomycin, or gentamicin for six weeks. For children under eight years, gentamicin, streptomycin, or rifampicin are added to tri-

methoprim-sulfamethoxazole (19). One study reported that the most commonly used treatment regimen was the combination of trimethoprim-sulfamethoxazole and rifampicin (35). In our study, the most frequent treatment was a combination of rifampicin and trimethoprim-sulfamethoxazole (18%). The next most common regimen (15%) was rifampicin and trimethoprim-sulfamethoxazole with the addition of gentamicin for the first five days.

The limitations of our study include its retrospective nature and the relatively small patient sample. Additionally, since our hospital is a district hospital, patients requiring advanced diagnostic tests and treatment were referred to other facilities, and their follow-ups could not be conducted.

Conclusion

Hematopoietic system involvement is common in pediatric brucellosis, and hematological complications show a wide distribution according to the severity of the disease. In endemic regions like ours, brucellosis should be considered in febrile cases accompanied by rheumatological symptoms. Furthermore, the tube agglutination test value, which guides the diagnosis of brucellosis, can also provide an indication for patient hospitalization.

Ethics Committee Approval: This study was obtained from Van Research and Training Hospital Clinical Research Ethics Committee (Decision no: 2023/24-04, Date: 15.11.2023).

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