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Research Article

Brucellosis in childhood: retrospective evaluation of 37 cases and review of the literature

Çocukluk çağında bruselloz: 37 olgunun retrospektif değerlendirilmesi ve literatürün gözden geçirilmesi

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Abstract

Introduction: The aim of this study is to evaluate the demographic, clinical and laboratory characteristics and treatment results of pediatric patients followed up with the diagnosis of brucellosis in our clinic.

Methods: Patients who were followed up with the diagnosis of brucellosis in Kayseri Training and Research Hospital, Pediatric Infectious Diseases Clinic between October 2016 and December 2018 were retrospectively analyzed.

Results: A total of 37 patients, 26 (70.3%) male, were included in the study. The mean age of the patients whose ages ranged from 1 to 17 years was 9.3±4.3 years. Unpasteurized milk and/or dairy products were consumed in 86.5% of the patients and 48.6% had a family history of brucellosis. Joint pain (75.7%) was the most common presenting complaint. In the laboratory evaluation, 8.1% of the patients had leukopenia, 2.7% had thrombocytopenia and 21.4% had ALT elevation. Doxycycline plus rifampicin (43.2%) was the most commonly preferred treatment regimen. Addition of aminoglycoside to initial therapy in hospitalized patients was statistically higher than in outpatients (81.2% vs. 23.8%) (p=0.001). During the follow-up, relapse developed in a total of 4 (10.8%) patients, 3 of whom were outpatients. There was no statistical relationship between the initial treatment regimen and relapse (p=0.418).

Conclusion: In conclusion, brucellosis should be kept in mind in terms of differential diagnosis in patients who present with joint pain in our country and who have cytopenia and/or isolated aminotransferase elevation in their investigations.

Keywords: Child, Brucellosis, Leukopenia, Relapse, Thrombocytopenia

Öz

Giriş: Bu çalışmada, kliniğimizde bruselloz tanısıyla takip edilen hastaların demografik, klinik, laboratuvar özellikleri ve tedavi sonuçlarını değerlendirmeyi amaçladık.

Yöntem: Kayseri Eğitim ve Araştırma Hastanesi, Çocuk Enfeksiyon Hastalıkları Kliniği'nde Ekim 2016-Aralık 2018 tarihleri arasında bruselloz tanısıyla takip edilen hastalar retrospektif olarak incelendi.

Bulgular: Çalışmaya 26'sı (%70.3) erkek toplam 37 hasta alındı. Yaşları 1 ile 17 arasında değişen hastaların yaş ortalaması 9.3±4.3 yıldı. Hastaların %86.5'inde pastörize edilmemiş süt ve/veya süt ürünü tüketimi, %67.6'sında ailede hayvancılık ve %48.6'sında da ailede bruselloz öyküsü vardı. Eklem ağrısı (%75.7) en sık başvuru yakınması olarak saptandı. Laboratuvar değerlendirilmesinde hastaların %8.1'inde lökopeni, %2.7'inde trombositopeni ve %21.4'ünde ALT yüksekliği vardı. Tedavide doksisiklin artı rifampisin (%43.2) en sık tercih edilen rejimdi. Hastanede yatan hastalarda başlangıç tedavisine aminoglikozid eklenmesi, ayaktan hastalara göre istatistiksel olarak daha yüksekti (%81.2'ye karşı %23.8) (p=0.001). Takipte 3'ü ayaktan takip edilen olgular olmak üzere toplam 4 (%10.8) hastada relaps gelişti. Başlangıç tedavi rejimi ile relaps arasında istatistiksel bir ilişki yoktu (p=0,418).

Sonuç: Sonuç olarak, ülkemizde eklem ağrısı yakınmasıyla başvuran tetkiklerinde sitopeni ve/veya izole aminotransferaz yüksekliği saptanan hastalarda bruselloz ayırıcı tanılar açısından akılda tutulmalıdır.

Anahtar kelimeler: Çocuk, Bruselloz, Lökopeni, Relaps, Trombositopeni

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Key Points

1. In brucellosis, initiation of inpatient treatment and strict control of treatment may improve adherence to treatment and reduce relapse rates.

Introduction

Brucella infection, which is common in Turkey, is an important zoonotic disease that can be transmitted by direct contact from infected animals to humans, and by consuming fresh unpasteurized milk and dairy products, and is an important zoonotic disease that threatens both animal health and public health [1].

Brucella species are aerobic gram-negative coccobacilli. Brucella melitensis (goat/sheep), Brucella abortus (cattle), Brucella suis (pig), and Brucella canis (dog) are common agents in humans [2]. The onset in children is insidious and includes fever, night sweats, weakness, loss of appetite, weight loss, arthralgia, myalgia, back pain, abdominal pain, and headache [3]. The presence of an individual with similar symptoms in the family, whether the family is engaged in animal husbandry, and the history of consuming unpasteurized milk and dairy products should be asked [4]. Anemia, leukopenia, thrombocytopenia or, less frequently, pancytopenia are hematological findings that may suggest the diagnosis [3]. Antimicrobial therapy reduces morbidity, shortens the course of the disease and reduces the incidence of brucellosis complications [5]. Long-term treatment is required for cure. Since monotherapy is associated with a high rate of recurrence, combination therapy is recommended as a standard [3]. Most patients with brucellosis recover completely after receiving adequate treatment. Despite appropriate treatment, relapses may occur in some patients [5].

In this study, we aimed to evaluate the demographic, clinical, laboratory characteristics and treatment results of the patients treated in our clinic, together with the data of our country.

Methods

Study design and data collection

The data of all patients who were followed up with a diagnosis of brucellosis in the Pediatric Infectious Diseases Clinic of Kayseri Training and Research Hospital between October 2016 and December 2018 were retrospectively analyzed through the Hospital Information Management System. Definitive diagnosis of brucellosis; it was defined as the presence of a Wright agglutination titer of ≥1/160 in the patient and/or the production of Brucella spp. in the culture sample (blood, bone marrow, cerebrospinal fluid (CSF), synovial fluid). Data of patients with brucellosis diagnosis, such as age, gender, admission complaint-physical examination findings and treatment applied, were recorded in the case form. Hemogram parameters, aspartate aminotransferase (AST), alanine aminotransferase (ALT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), Brucella agglutination results of all patients were recorded. Culture (blood, bone marrow, CSF, synovial fluid) results of the hospitalized patients were recorded. From the hematological parameters, anemia was defines as hemoglobin level <10 g/dL, leukopenia; total leukocyte count <5000/mm³, thrombocytopenia; thrombocyte (PLT) count below 150.000/mm³ and pancytopenia was defined as low in all three series. Relapse was defined as recurrence of symptoms after completion of treatment and increase in 2-mercaptoethanol (2-ME) agglutination test titer.

Ethical approval

Ethics committee approval dated 11.12.2019 and numbered 2019/20 was obtained from the local ethics committee.

Statistical analysis

SPSS program (version 23.0, IBM Company, SPSS Inc.) was used for statistical analysis. While defining the participant baseline characteristics, descriptive statistics such as mean±standard deviation (SD), median and range (smallest value-maximum value) according to whether the data were parametric or not, and frequency (n) and percentage (%) were used for categorical variables. The normality of the distribution of continuous variables was evaluated with the Shapiro-Wilks test. We compared by t-test for independent samples if the assumption of normality was met, otherwise by non-parametric Mann-Whitney U. Categorical data were compared with the Chi-Square test. Cases with a type 1 error level below 5% were interpreted as statistically significant.

Results

A total of 42 patients were included in the study. Thirty-seven patients were analyzed **(Figure-1)**. Twenty-six (70.3%) of 37 patients followed up with a diagnosis of brucellosis were male. The mean age (±SD) of the patients whose ages ranged from 1 to 17 years was 9.3±4.3 years. Unpasteurized milk and/or dairy products were consumed in 32 (86.5%) patients, there was a family history of animal husbandry in 25 (67.6%) and a family history of brucellosis in 18 (48.6%) patients.

Joint pain was found to be the most common complaint with a rate of 75.7% and fever with a rate of 18.9%. The patients presented most frequently in the spring and autumn with 29.7%, followed by winter (21.6%) and summer (19%), respectively.

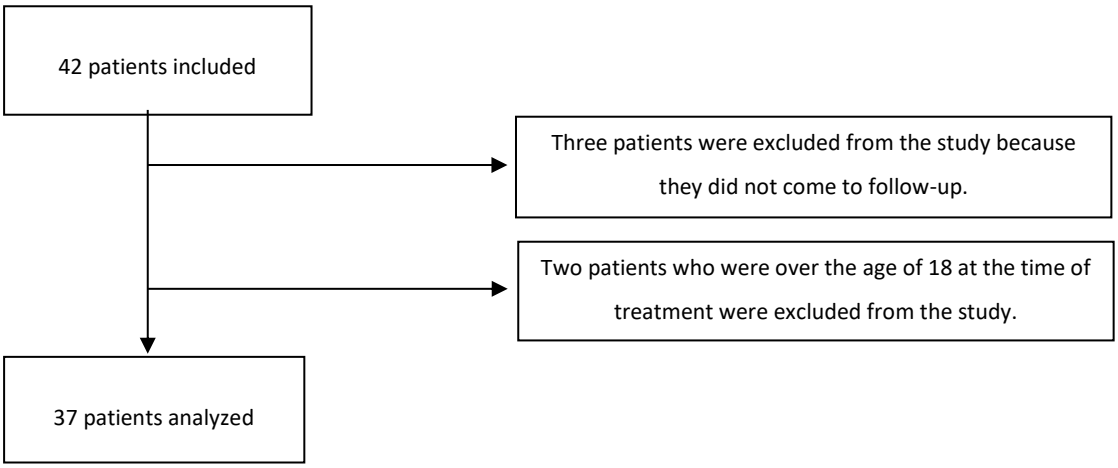

Figure 1. Flow chart showing the patients included in the study. A total of 42 patients were included in the study. Thirty-seven patients were analyzed.

In the laboratory evaluation of admission, mean (±SD) total leukocyte 7.720±2.688/mm³, neutrophil 3.510±2.116/mm³, lymphocyte 3.499±1.434/mm³, PLT 275.378±67.104/mm³, Hb 12.5±1.4 g/dL, CRP 13.9 ±3.83 mg/dL and ESR were found to be 17.2±1.7 mm/h. Three (8.1%) patients had leukopenia, 1 (2.7%) thrombocytopenia, and 1 (2.7%) anemia. Alanine aminotransferase was elevated in 21.4% and AST was elevated in 10.7% of the patients. White blood cell (WBC), neutrophil, lymphocyte, monocytes, eosinophil, platelet counts, mean platelet volume (MPV), platelet distribution range (PDW), plateletcrit (PCT), ALT, AST, CRP and ESR values of outpatients and inpatients were compared **(Table 1)**. There was no statistically significant difference between the laboratory values of the outpatients and inpatients (p>0.050). Rose Bengal and agglutination test were positive in serum in all patients. Brucella agglutination titer ranged from 1/160 to 1/10240. Twenty (54%) patients were hospitalized and followed up. Brucella melitensis was isolated from blood cultures of three (15%) hospitalized patients. It was also isolated in the joint fluid culture of a patient with arthritis and in the bone marrow culture of a patient who underwent bone marrow aspiration due to bicytopenia.

Sixteen (43.2%) of the cases were doxycycline plus rifampicin, 11 (29.7%) doxycycline plus rifampicin plus gentamicin, 7 (18.9%) trimethoprim/sulfamethoxazole plus rifampicin plus gentamicin, and 3 (8.2%) trimethoprim-sulfamethoxazole plus rifampicin treatments were given. Addition of aminoglycoside to initial therapy in hospitalized patients was statistically higher than in outpatients (81.2% vs. 23.8%) (p=0.001). The overall aminoglycoside utilization rate was 48.6%. During the follow-up, relapse developed in 4 (10.8%) cases, 3 of which were outpatients, and the treatment was either not used regularly or stopped early in all cases. All of these cases were given 6 weeks of triple combined therapy according to their age, which included aminoglycosides for the first 2 weeks of treatment. There was no statistical relationship between the initial treatment regimen and relapse (p=0.418). Hemophagocytic lymphohistiocytosis (HLH) developed in one of our patients during follow-up, one of our patients was followed up for neurobrucellosis, no mortality was observed.

Table 1. Laboratory characteristics at the time of diagnosis, rates of aminoglycoside use and treatment outcomes of inpatients and outpatients

	INPATIENT (n=16)	**OUTPATIENT (n=21)**	
	Mean±SD or Median (Min.-Max.) (n,%)	**Mean±SD or Median (Min.-Max.) (n,%)**	**p***
Laboratory			
WBC (/mm³)	7650 (3780-14540)	6590 (4930-12280)	0.961
Neutrophils (/mm³)	2525 (1160-11610)	3080 (1790-7900)	0.714
Lymphocytes (/mm³)	3523±1518	3480±1405	0.821
Monocytes (/mm³)	540 (300-1100)	515 (200-970)	0.922
Eosinophil (/mm³)	15 (0-130)	110 (10-830)	0.339
Platelets (/mm³)	264125±72649	283952±62996	0.337
MPV (fL)	9.2± 0.67	9.14±0.73	0.404
PDW (%)	9 (7.7-14.2)	9.4 (8-12)	0.378
PCT (%)	0.25±0.09	0.25±0.05	0.516
CRP (mg/dl)	6.42 (3-131)	3.23 (3-33)	0.903
ESR (mm/h)	17.2 (4-55)	17.2 (2-40)	0.370
Use of Aminoglycosides	13 (81.2%)	5 (23.8%)	0.001
Relapse	1 (6.2%)	3 (14.2%)	-

WBC, white blood cell; **CRP**, C-reactive protein; **ESR**, erythrocyte sedimentation rate; **MPV**, mean platelet volume; **PDW**, platelet distribution width; **PCT**, plateletcrit; **SD**, standard deviation
* Mann-Whitney U or t-test or Chi-Square

Discussion

In our study, male gender, frequency of joint pain, low leukopenia and thrombocytopenia were the prominent features. Brucellosis may be more common in children in developing countries due to unpasteurized milk and livestock activities [6,7]. It is a common zoonotic disease in our country and is endemic [2]. People of all ages and genders are susceptible to brucellosis. However, approximately 11-56% of patients affected by brucellosis in endemic regions are younger than 14 years of age [6,7]. In 18 studies conducted in our country in 2011 and after, in which children aged <18 years were evaluated, the mean age ranged between 7.3-11.9 years (Table 2) [7-24]. In the reports, male case rates are generally between 30-69.3% [25-27], in our country, apart from 3 studies reporting this rate as 45-46.8% [10,11,17], male predominance is observed with a rate of 54.4-75% in 15 studies (Table 2) [7-24].

Hematological complications such as anemia, leukopenia and thrombocytopenia are common in the course of brucellosis, and pancytopenia may be observed less frequently [3,5]. These hematological complications are more common in acute brucellosis cases (as opposed to relapse cases) and in patients with growth in blood culture [28]. These complications are typically mild and resolve promptly with antimicrobial therapy. Rarely, thrombocytopenia may be severe and cause bleeding in the skin and mucosal areas [5]. Studies among hematological findings report 7.4-40.3% leukopenia, 2.4-26.9% thrombocytopenia and 2-21% pancytopenia (Table 2) [7-28]. Brucellosis should be considered at the time of diagnosis in patients with pancytopenia in endemic areas and diagnosed with immune thrombocytopenic purpura [6]. Since pancytopenia is a rare finding, other possible etiologies (leukemia, etc.) should be kept in mind [29]. The relatively low rates of leukopenia and thrombocytopenia in our study may be related to the low rate of bacteremia in our patients.

Although aminotransferase levels are normal or slightly elevated in most patients with brucellosis, the liver, the largest organ of the reticuloendothelial system, is always affected in brucellosis. Rarely, it may present with acute hepatitis with aminotransferase levels resembling viral hepatitis [5,6]. Brucellosis-related hepatitis was reported in only 4 studies [7,17,20,23] conducted in our country. Transaminase elevation, which was reported as 35-75% in international studies, was higher than the rates reported in our country (17.3%-54.6%) (Table 2) [7-27]. We thought that the reason for this might be due to the early diagnosis of brucella being endemic in our country.

Antimicrobial therapy reduces morbidity, shortens the course of the disease and reduces the incidence of brucellosis complications [5]. Long-term treatment is required for cure. Due to the high rate of relapse in monotherapy, combination therapy with two or more antibiotics is recommended as standard [2,3]. Classically, oral doxycycline plus rifampicin is used in children over 8 years of age, and oral trimethoprim-sulfamethoxazole plus rifampicin in children younger than 8 years old for at least 6 weeks [3,6]. Since in vitro killing of bacteria can be increased by adding an aminoglycoside to the treatment, a triple treatment regimen can be used by adding gentamicin for 7-14 days in severe infections [3,5]. When evaluated by ignoring the severity of the disease in studies conducted in our country, the rate of preference for aminoglycosides in treatment (two or three) varies between 1.3 and 93.9% (Table 2), while it is reported that this rate reaches 100% in international studies [7-27].

Most patients with brucellosis recover completely after receiving adequate treatment. Despite appropriate treatment, relapses may occur in some patients [5]. Relapses usually occur within the first six months after treatment and are usually due to early discontinuation of therapy rather than drug resistance. Triple therapy is applied in relapses [2]. Although the relapses rate was reported as 1.3-7.9% in studies conducted in our country, it has been reported that this rate is quite high, such as 20-31%, in international studies in which dual treatment regimens with aminoglycosides are used more frequently [7-27]. Pediatricians following children with brucellosis should educate patients and their families about improving adherence to prescribed antibiotic regimens and evaluating treatment outcomes through strict long-term follow-up [6]. Our observation was that the relapse rate was lower in hospitalized patients (we could not perform statistical analysis due to the small number of patients). We attributed this to the increase in adherence to treatment due to the severity of the disease requiring hospitalization. For this reason, we think that initiation of inpatient treatment and tight control of treatment may increase adherence to treatment and reduce relapse rates.

Table 2.1. Patient characteristics and articles published in Turkey in our study

Study/ Publication Year		Number of Cases (n)	Mean Age (Year)	Male Gender (%)	Family History (%)	Unpasteurized Milk Consumption (%)	Fever (%)	Joint Pain (%)	Arthritis (%)	Neurobrucellosis (%)	Complication
Çataklı (8)	2011	33	10.5	75	-	85	73	87	42	-	-
Çelebi (9)	2011	62	10	62.9	32.3	51.6	88.7	64.5	29	8.1	Brain abscess
Öncel (10)	2011	24	11.2	45.8	33.3	53.3	93.3	53.3	46.6	-	-
Abuhandan (11)	2011	82	11.9	45	-	73	92	75.9	26.8	2.4	Brain abscess
Uluğ (12)	2011	22	8.9	63.6	-	72.7	90.9	54.6	22.8	-	-
Okur (13)	2011	147	9.14	54.4	-	100	38.8	61.2	13.6	-	-
Yoldaş (14)	2014	97	10	55.7	33	80.4	78.4	76.3	23.7	3	Osteomyelitis, Pneumonia
Parlak (15)	2015	496	10	61	-	-	32.1	46.2	10.1	-	-
Çıraklı (16)	2015	52	11	80.8	32.7	75	75	58.3	19.2	-	Osteomyelitis
Kara (17)	2016	94	8.85	46.8	30.8	87.2	88.2	85.1	12.7	1.1	Hepatitis
Bozdemir (18)	2017	60	10.8	81.7	-	-	100	93.3	28.3	-	-
Yüksel (19)	2019	50	11.3	72.5	30	82.5	62.5	56.3	26.3	3.8	HSP, ITP
Gündeşlioğlu (20)	2019	148	10.1	58.8	39.2	4.1	59.5	41.2	6.7	-	Sacroileitis, Epididymitis, Hepatitis
Büyükçam (21)	2020	60	9.3	58.3	-	-	11.7	83.3	-	-	-
Çiftdoğan (22)	2020	202	7.37	60	-	-	77	26.2	21	-	Osteomyelitis
Bayhan (23)	2020	98	10.1	75	-	56	-	68	1	2	Pneumonia, Hepatitis, Osteomyelitis
Karaman (24)	2021	73	10.2	58	28	90.6	94	75	29	1.3	HLH, Epididymo-orchitis, Sacroileitis, Focal abscess
Özcanaslan (7)	2021	65	8.65	58.5	38.5	92.3	81.5	38.5	20	1.5	Hepatitis
Our study		37	9.3	70.3	48.6	86.4	18.9	75.6	18.9	2.7	HLH, Sacroileitis

HLH, hemophagocytic lymphohistiocytosis; **ITP**, immune thrombocytopenic purpura

Table 2.2. Patient characteristics and articles published in Türkiye in our study

Study/ Publication Year		Leukopenia (%)	Thrombocytopenia (%)	Pancytopenia (%)	Increased CRP (%)	Increased ESR (%)	Increased ALT/AST (%)	Positive Blood Culture (%)	Aminoglycoside Usage Rate (%)	Relapse (%)
Çataklı (8)	2011	-	3	-	63.6	84.8	-	6	-	-
Çelebi (9)	2011	12.9	6.5	-	40.3	51.6	42	25.6	76.1	4.8
Öncel (10)	2011	-	-	-	72	63.1	17.3	30.7	37	6.6
Abuhandan (11)	2011	10.9	2.4	-	65.9	85.5	31.7	2.4	17	-
Uluğ (12)	2011	18.2	13.6	4.5	86.3	90.9	36.4/54.6	9	-	4.5
Okur (13)	2011	13.6	9.5	3.4	63.9	51	25.9/34	2	-	-
Yoldaş (14)	2014	9.4	14.4	-	45.4	73.2	35.6/41.3	48.4	29	2
Parlak (15)	2015	12.1	15.5	4	58.7	55.2	30.3/42.4	3.7	-	-
Çıraklı (16)	2015	40.3	26.9	21	68	48	26.9/34.6	56.1	-	-
Kara (17)	2016	7.4	-	2	-	-	-	-	-	7.4
Bozdemir (18)	2017	-	+	3.3	-	-	-	32.7	38	-
Yüksel (19)	2019	21.3	15.5	5	-	-	38	17.5	14	-
Gündeşlioğlu (20)	2019	8	4.8	-	-	-	21.4	72	-	1,3
Büyükçam (21)	2020	-	-	-	-	-	-	15	-	-
Çiftdoğan (22)	2020	13	9	-	-	-	-	33	24	7.9
Bayhan (23)	2020	Cytopenia: 10%			-	-	-	-	7	-
Karaman (24)	2021	17	15	9	56	62	49	28	1.3	-
Özcanaslan (7)	2021	21.5	21.5	12.3	50.8	43	37.5	47.8	93.9	-
Our study		8.1	2.7	-	37.8	18.9	21.4/10.7	15	48.6	10.8

CRP, C-reactive protein; **ESR**, erythrocyte sedimentation rate; **ALT,** alanine aminotransferase**; AST,** aspartate aminotransferase

Limitations

The limitations of our study are its retrospective nature and the relatively small sample size of patients.

Conclusion

In conclusion, brucellosis can cause serious morbidity in humans and remains an important health problem in Turkey. In our country, it is very important to keep brucellosis in mind in the differential diagnosis of patients presenting with joint pain, cytopenia and/or isolated aminotransferase elevation, and to perform family screening for early diagnosis in the presence of a family member with brucellosis. In addition, considering that relapses are caused by the problem of adherence to treatment, it is clear that there is a need to develop new strategies to increase adherence to treatment during the long treatment period.

Conflict of interest: The authors declare no conflict of interest.

Author Contributions		Author Initials
SCD	Study Conception and Design	TÇ, EK
AD	Acquisition of Data	TÇ, EK
AID	Analysis and Interpretation of Data	TÇ, EK
DM	Drafting of Manuscript	TÇ, EK
CR	Critical Revision	TÇ, EK

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