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RESEARCH

Hepatobiliary involvement in patients with brucellosis

Brusellozlu hastalarda hepatobiliyer tutulum

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Abstract

Purpose: Brucellosis is a common infectious disease in many countries worldwide and endemic in some regions. This study aimed to investigate the frequency and characteristics of hepatobiliary involvement in pediatric patients diagnosed with and treated for brucellosis.

Materials and Methods: A total of 71 patients who were diagnosed with brucellosis and received treatment between 2022 and 2024 were retrospectively evaluated. Clinical and demographic characteristics, along with laboratory parameters, were collected through a review of the patients' medical records. Rose Bengal test positivity, Wright agglutination titers, and culture results were reviewed.

Results: The mean age of the patients was 126 months. Of the patients, 42.3% were females and 57.7% were males. The median aspartate aminotransferase (AST) value was 61.5 IU/L (range: 14-125), and the median alanine aminotransferase (ALT) value was 71 IU/L (range: 6-256). The most common complaints were myalgia, arthralgia, and low back pain, while weight loss and headache were the least frequent symptoms. In terms of physical examination findings, the majority of cases showed normal results, with arthritis being the most common pathological finding. Among the patients, 22 (31%) had elevated ALT levels, 31 (43.7%) had elevated AST levels, and 20 (28.2%) had elevated levels of both AST and ALT. Of the patients (n=20) with AST and ALT levels of >40 IU/L, the standard tube agglutination test (STAT) titer was below 1/1280 in 6 patients and ≥1/1280 in 14 patients. Elevated transaminases returned to normal in all patients after treatment. Hepatomegaly or splenomegaly was detected in 8 (11.2%) and 2 (2.8%) patients, respectively.

Conclusion: Brucellosis affects multiple organ systems, and its clinical manifestations can vary widely. Due to frequent occurrence of hepatobiliary involvement in brucellosis, brucellosis should always be considered in the differential diagnosis of elevated transaminases, hepatomegaly, and splenomegaly.

Keywords:. Brucellosis, child, hepatobiliary involvement

Öz

Amaç: Bruselloz, dünyada birçok ülkede görülen ve bazı bölgelerde endemik olan bir enfeksiyon hastalığıdır. Bu çalışmada brusella tanısı konan ve tedavisi planlanan çocuk hastalarda hepatobiliyer tutulum sıklığı ve özellikleri araştırılması amaçlanmıştır.

Gereç ve Yöntem: 2022-2024 tarihleri arasında bruselloz tanısı konulup tedavi uygulanan 71 hasta geriye dönük olarak değerlendirildi. Dosya kayıtları incelenerek klinik, demografik özellikleri, laboratuar parametreleri kaydedildi. Hastaların Rose Bengal pozitifliği, Wright aglütinasyon titresi ve kültür sonuçları değerlendirildi.

Bulgular: Hastaların yaş ortalaması 126 ay ve %42,3'si kız, %57,7'si erkek idi. Olguların AST ortanca değeri 61.5 IU/L (14-125), ALT ortanca değeri 71 IU/L (6-256) idi. Olguların en sık şikayeti kas, eklem ve bel ağrısı iken, en az şikayet kilo kaybı veya baş ağrısı idi. Olgularda en sık normal fizik muayene bulguları saptanırken, patolojik en sık fizik muayene bulgusu artritti. Olguların 22'sinde (%31) ALT yüksekliği, 31'inde (%43.7) AST yüksekliği ve 20'sinde (%28.2) olguda AST ve ALT yüksekliği saptandı. Standart tüp aglutinasyon titresi 1/1280 altında ASTve ALT >40 hasta sayısı 6 iken, 1/1280 ve üstünde hasta sayısı 14 idi. Transaminaz yüksekliği tedavi sonrası normale döndü. 8 (%11.2) hastada hepatomegali, 2(%2.8) hastada splenomegali saptandı.

Sonuç: Bruselloz birçok sistemi etkileyip, klinik bulgular farklı olabilir. Eşlik eden hepatolojik tutulumun sık görülmesi nedeni ile transaminaz yüksekliği, hepatomegali ve splenomegalinin ayırıcı tanısında bruselloz mutlaka akılda tutulmalıdır.

Anahtar kelimeler: Bruselloz, çocuk, hepatobiliyer tutulum

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INTRODUCTION

Brucellosis is a zoonotic bacterial infectious disease that is prevalent in many countries worldwide and endemic in some regions[1]. Although 150,000 to 250,000 cases of human brucellosis are reported annually worldwide, reliable data on its incidence in low-income countries remain unavailable[2]. It is transmitted to humans through direct contact with infected animal secretions, compromised skin integrity, or consumption of unpasteurized milk and dairy products. Childhood brucellosis accounts for 10-30% of cases [3].

Brucellosis is a systemic disease that can be particularly challenging to diagnose in children. Symptoms can be acute or insidious, and are often nonspecific. Many organs or systems can be affected. *Brucella* infection can involve any organ or tissue in the body. The most commonly affected systems include the musculoskeletal, gastrointestinal, genitourinary, hematological, cardiovascular, respiratory, and central nervous systems [4]. Brucellosis is considered in the differential diagnosis of numerous diseases due to its diverse clinical presentations. The disease can pose challenges in diagnosis, treatment, and management, particularly when complications arise. Its clinical spectrum ranges from asymptomatic cases to severe systemic infections. Brucellosis may manifest with systemic symptoms and signs such as fever, fatigue, joint pain, headache, sweating, anorexia, weight loss, lymphadenopathy, and hepatosplenomegaly[5]. The liver, being the largest organ of the reticuloendothelial system, can also be affected in brucellosis. Mild elevations in transaminases and hepatomegaly may occur during the course of the disease.

Brucellosis remains a major global health concern, requiring a multidisciplinary approach for its management[6]. Brucellosis remains a significant public health concern, particularly in developing countries, where reliable data on its incidence and related complications are often limited. This study focused on the prevalence and characteristics of hepatobiliary involvement in pediatric patients diagnosed with brucellosis. By reviewing the medical records, including routine examinations, laboratory investigations, and treatment procedures, this study aims to contribute valuable data on brucellosis-related liver complications in children, thereby enhancing understanding of its impact in regions where data is scarce and aiding in the development of more effective management strategies.

MATERIALS AND METHODS

Sample

The study sample consisted of 71 children, aged between 6 months and 18 years, who were diagnosed with brucellosis at the Department of Pediatric Infectious Diseases at Adana City Education and Research Hospital between 2022 and 2024. All included patients had complete follow-up and file records. The patients' data were reviewed by a pediatric infectious disease specialist and a pediatric gastroenterologist. Patients aged 6 months to 18 years who met the diagnostic criteria for brucellosis were included in the study. Out of 84 patients with available file records, 13 were excluded due to incomplete medical records or lack of follow-up.

Procedure

Ethical approval was obtained from the Clinical Research Ethics Committee of Adana City Research and Training Hospital (15.02.2024/No: 3180). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Medical records were retrospectively reviewed, and data including age at diagnosis, sex, nutritional status, clinical symptoms and findings, complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), liver enzyme levels (aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), total protein, albumin, total/direct bilirubin), and abdominal ultrasound findings were noted. The diagnostic criteria for brucellosis included clinical symptoms consistent with disease, along with Rose Bengal test positivity and/or a significant Wright agglutination titer of 1/160 or higher, or isolation of *Brucella* spp. from cultures.

When assessing hepatobiliary involvement, the presence of any of the following was considered sufficient: (1) serum ALT >40 U/L and serum AST >40 U/L; (2) detection of clinical hepatomegaly confirmed by ultrasonography; (3) Abnormal ultrasonographic findings other than hepatomegaly. Serum AST and ALT levels <40 U/L were

considered normal [7]. Patients with other bacterial, viral, and fungal infections, chronic diseases, or incomplete examination and laboratory data in their medical records were excluded from the study. Additionally, patients with common liver diseases such as viral hepatitis, metabolic disorders, autoimmune liver diseases, biliary diseases, or neoplastic conditions potentially associated with elevated liver enzymes were excluded. Only patients who met the inclusion criteria and had complete medical records were included in the study.

Statistical Analysis

All statistical analyses were conducted using SPSS version 20.0 (IBM Corp., Armonk, NY). Categorical variables were expressed as numbers and percentages, while continuous variables were summarized as median and range (min-max).

RESULTS

A total of 71 patients diagnosed with brucellosis were included in the study. Among them, 30 (42.3%) were girls and 41 (57.7%) were boys. The mean age of the patients was 126 months (range: 26-213 months). Musculoskeletal pain, arthralgia and back pain were reported in 58 (81.7%) patients, while fever was present in 38 (53.5%) patients. Weight loss and headache were the least common presenting symptoms.

Table 1. Demographic characteristics of the patients with brucellosis

Characteristic	**n (%)**
Age (months)	126 (26-213)
Sex	
Male	41 (57.7%)
Female	30 (42.3%)
Presenting symptom	
Myalgia, arthralgia and low back pain	58 (81.7%)
Fever	38 (53.5%)
Fatigue	21 (29.6%)
Abdominal pain	12 (16.9%)
Weight loss	5 (7.1%)
Headache	1 (1.4%)
Duration of presenting symptoms (days)	30 (5-180)
Consumption of unpasteurized milk and dairy products	
Yes	61 (85.9%)
No	10 (14.1%)
Affected household members	
Yes	34 (47.9%)
No	37 (52.1%)
Findings	
Normal	42 (59.1%)
Arthritis	11 (15.4%)
Hepatomegaly	9 (12.6%)
Fever	7 (9.8%)
Lymphadenopathy	4 (5.6%)
Central nervous system involvement	3 (4.2%)
Splenomegaly	2 (2.8%)
Hospitalization	
Yes	6 (8.5%)
No	65 (91.5%)
Relapse	
Yes	1 (1.4%)
No	70 (98.6%)

The average duration of presenting symptoms was 30 days (range: 5-180 days). Ingestion of unpasteurized milk and dairy products was reported in 61 (85.9%) patients. Household members of these 61 patients were also affected by brucellosis (Table 1). Initial physical examination at the time of presentation most commonly showed normal findings (59.1%), while arthritis was the most prevalent pathological finding (15.4%). Hepatomegaly was observed in 9 (12.6%) patients, and splenomegaly in 2 (2.8%) patients. Six patients required hospitalization for treatment. Demographic data of the patients are presented in Table 1. All patients tested positive for the Rose Bengal test, and Wright agglutination test of each patient showed a titer of 1/160 or higher.

The median AST value was 61.5 IU/L (range: 14-125), and the median ALT value was 71 IU/L (range: 6-256). Laboratory parameters of the patients are shown in Table 2. Elevated ALT levels were observed in 22 (31%) patients, elevated AST levels in 31 (43.7%) patients, and elevated levels of both AST and ALT in 20 (28.2%) patients (Table 3). Total bilirubin levels were elevated in three patients (4.2%), and elevated direct bilirubin levels were found in two patients (2.8%). Liver biopsy was not performed in any of the patients. Among the patients with an AST of >40 IU/L, the standard tube agglutination test (STAT) titer was below 1/1280 in 10 patients, and ≥1/1280 or higher in 18 patients. In patients with an ALT of >40 IU/L, the corresponding numbers were 8 and 14, respectively. For patients with both AST and ALT >40 IU/L, the STAT titer was below 1/1280 in 6 patients and ≥1/1280 or higher in 14 patients (Table 4). None of the patients showed hypoalbuminemia or prolongation of prothrombin time. Elevated transaminases returned to normal in all patients after treatment. A review of abdominal ultrasound findings revealed hepatomegaly in 8 (11.2%) patients, splenomegaly in 2 (2.8%) patients, and normal findings in 31 (43.6%) patients.

Table 2. Laboratory results of patients with brucellosis

Parameter	Median (min-max)
White blood count (cells/mm^3)	6050 (4.400-11.700)
Hemoglobin (g/dL)	12.45 (10-13.60)
Platelet count (cells/mm^3)	227.500 (142.000-538. 000)
CRP (mg/dL)	6.95 (0.20-150.70)
ESR (mm/h)	13.50 (2-59)
AST (>40 IU/L)	61.50 (14-125)
ALT (>40 IU/L)	71 (6-256)
ALP (range: 50-350 IU/L)	185.5 (63-340)
GGT (range: 0-60 IU/L)	22.50 (9-60)
Total bilirubin	0.40 (0.20-2.50)
Direct bilirubin	0.10 (0.04-1.80)
Total protein	7.05 (6-7.80)
Albumin	4 (3.50-5)
STAT positivity	
1/160	5 (7%)
1/320	7 (9.9%)
1/640	20 (28.2%)
1/1280	31 (43.7%)
1/2560	5 (7%)
1/5120	1 (1.4%)
1/10240	2 (2.8%)

AST, aspartate aminotransferase; ALT, alanine transaminase; ALP, alkaline phosphatase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GGT, gamma-glutamyl transferase; STAT: standard tube agglutination test.

Table 3. Distribution of elevated transaminase levels

ALT and AST	n (%)
ALT > 40 U/L	22 (31%)
AST > 40 U/L	31 (43.7%)
ALT > 40 U/L and AST > 40 U/L	20 (28.2%)

AST, aspartate aminotransferase; ALT, alanine transaminase.

Table 4. Distribution of STAT positivity by elevated transaminases

STAT positivity	AST>40 IU/L	ALT>40 IU/L	AST and ALT>40
1/160	1 (1.4%)	1 (1,4%)	0 (0%)
1/320	2 (2.8%)	2 (2.8%)	1 (1.4%)
1/640	7 (9.9%)	5 (7%)	5 (7%)
1/1280	16 (22.5%)	11 (15.5%)	11 (15.5%)
1/2560	3 (4.2%)	2 (2.8%)	2 (2.8%)
1/5120	0 (0%)	0 (0%)	0 (0%)
1/10240	2 (2.8%)	1 (1.4%)	1 (1.4%)
Total	31 (43.7%)	22 (31%)	20 (28.2%)

AST, aspartate aminotransferase; ALT, alanine transaminase; STAT: standard tube agglutination test.

DISCUSSION

Brucellosis is a systemic disease endemic in the Mediterranean countries, presenting with a variety of clinical signs and symptoms, which makes its diagnosis and treatment challenging. *Brucella* species infecting humans include *Brucella melitensis*, *Brucella abortus*, *Brucella suis*, and *Brucella canis*[8]. Following transmission, the bacteria multiply in regional lymph nodes and enter the bloodstream, leading to nonspecific symptoms that can mimic other diseases. The most common complaints include fever, arthralgia, and sweats[9]. The majority of patients experience dyspeptic symptoms resulting from gastrointestinal involvement. Heterogeneous nature of the clinical presentations of brucellosis contributes to diagnostic challenges. Without adequate treatment, the disease may evolve into chronic brucellosis, with possible occurrence of complications and relapses[10].

Brucellosis is a zoonotic infection that primarily affects the reticuloendothelial system (RES). It has a well-known predilection for the RES, manifesting as hepatitis, hepatomegaly, splenomegaly, and peripheral lymphadenopathy [11]. During the course of brucellosis, widespread liver involvement is commonly reported. Liver involvement varies, ranging from mild elevation in transaminase levels to mild hepatosplenomegaly, chronic suppurative disease, and, infrequently, acute hepatitis[12].

Liver involvement is common during the course of the disease. In a study including 325 patients with prominent hepatobiliary involvement, significant clinical hepatitis was found in 284 (87.3%), and cholestasis in 215 (66.1%) patients. Major symptoms included fatigue (91%), fever (86%), sweats (83%), joint pain (79%), and loss of appetite (79%) [13]. In a study by Tuba et al., hematological involvement was most commonly observed (44%), followed by liver involvement (20.7%), and osteoarticular involvement (10%), with elevated AST and ALT levels found in 16.2% and 20.7% of the patients, respectively [14]. In another study, liver involvement was detected in 2.5% (n=8) of 317 patients with brucellosis [15]. A study conducted in Türkiye found that 92 out of 248 patients diagnosed with brucellosis had liver involvement. Among those with liver involvement, 48% had hepatomegaly, and 33% had splenomegaly[16]. In a retrospective study of 60 patients with brucellosis, elevated transaminases were observed in 25% of the patients [17]. In a separate study evaluating 201 patients with brucellosis, elevated AST and ALT levels were reported in 41.7% and 36.8% of the patients, respectively [18]. A study involving 151 patients diagnosed with brucellosis, elevated AST and ALT levels were found in 15.9%

and 15.2% of the patients, respectively [19]. Transaminase elevation was reported at a prevalence of 15-57% in previous studies, and in our study, AST and ALT elevations were observed in 43.7% and 31% of the patients, respectively. Thus, our findings are consistent with the literature data. In a study by Şahintürk et al., elevated transaminases were detected in 70 of 195 patients with brucellosis before treatment, 26 of whom had blood cultures positive for *Brucella*. It was reported that positive blood culture and high serum agglutination titers are associated with hepatitis [7]. Likewise, in our study, elevated transaminases were associated with increased serum agglutination titers of 1/1280 or higher. The development of clinical hepatitis during the course of the disease has been shown to be associated with an abundance of bacteria in the liver. In a study of 1028 patients with brucellosis, elevated bilirubin levels, above 2.5 mg/dL, were observed in 1.6% of the patients [20].

Our study had some limitations. The major limitation was its retrospective, single-center design. As this was a retrospective study, patients could not be followed prospectively, hindering our ability to observe potential complications or relapses. Additionally, the small number of seropositive patients led to incomplete analyses. The limited sample size was another limitation.

In conclusion, brucellosis remains a significant public health problem in our country. Early diagnosis and treatment are crucial for effective management. Due to the nonspecific nature of its clinical presentation, the wide range of symptoms, and the involvement of multiple organ systems, brucellosis presents a challenge in endemic regions. It is essential to consider brucellosis in the differential diagnosis of elevated transaminases, hepatomegaly, and splenomegaly, particularly in patients residing in endemic regions, given the frequent co-occurrence of hepatobiliary involvement. These patients should be thoroughly evaluated for brucellosis to ensure timely and appropriate care.

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