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ORIGINAL ARTICLE

Challenging diagnosis in the COVID-19 era: Pediatric brucellosis - a retrospective observational study

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ABSTRACT

Objective: Brucellosis is the most common bacterial zoonotic disease worldwide, with an annual incidence of half a million cases. It predominantly affects rural areas of developing countries, and the actual disease burden is likely much higher than reported. This study aims to retrospectively evaluate the demographic, laboratory, and clinical characteristics of pediatric brucellosis cases in the pre- and post-COVID-19 era.

Material and Methods: Between April 1, 2019, and April 1, 2021, all children under 18 diagnosed with brucellosis at our secondary care hospital were retrospectively examined. Clinical, laboratory, and demographic data were retrieved from electronic medical records.

Results: Over the two-year study period, 59 children were diagnosed with brucellosis. The most common symptoms at presentation were arthralgia (81.4%) and fever (37.3%), with nearly two-thirds of the patients presenting as afebrile. Blood cultures were performed for 21 (35.6%) patients, with nine yielding positive results (42.9%). Patients with bacteremia were more likely to be admitted to the hospital and had higher C-reactive protein (CRP) levels and lower hemoglobin levels compared to non-bacteremic patients.

Conclusion: The symptoms of COVID-19 and brucellosis in children overlap, making the diagnosis of brucellosis particularly challenging in areas with low prevalence. It is crucial not to overlook brucellosis in afebrile patients, given the high proportion of children with brucellosis who do not present with fever. CRP levels may be indicative of bacteremia and the need for hospital admission.

Keywords: Brucellosis, COVID-19, CRP.

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INTRODUCTION

Brucellae are facultative intracellular gram-negative coccobacilli. Four *Brucella* species are known to cause infection in humans: *Brucella* canis, *Brucella* suis, *Brucella* melitensis, and *Brucella* abortus.[1] Transmission can occur through the consumption of raw milk and dairy products from infected animals, direct contact with infected animals, and droplet inhalation. Occupational exposure is also a major concern for laboratory staff.[2,3]

Brucellosis is the most common bacterial zoonotic disease worldwide, with half a million annual cases.[4] It is predominantly observed in the rural areas of developing countries, and the actual disease burden is believed to be significantly underreported.[5] The Mediterranean basin and the Middle East are the most affected regions, but brucellosis also occurs in Central Asia, China, the Indian subcontinent, sub-Saharan Africa, and Central and South America.[6] Although brucellosis is rare in developed countries, nearly one hundred new cases, mostly acquired abroad, are reported annually in the United States.[6]

Diagnosing brucellosis is challenging, as the disease's presentation, clinical, and laboratory findings are generally non-specific. This challenge is compounded in the COVID-19 era, where many clinical findings may overlap. Patients may present with a wide range of signs and symptoms, including but not limited to fever, arthralgia, myalgia, headache, hepatomegaly, splenomegaly, diarrhea, vomiting, and abdominal pain.

The definitive diagnosis of brucellosis is made by bacterial growth from blood, bone marrow, or other tissues. However, the utility of serological tests cannot be ignored, given that *Brucella* species grow slowly in blood culture, the specificity of blood culture is low, and access to blood culture is problematic in many low-resource healthcare settings in endemic regions. The most commonly used non-culture-based diagnostic test for brucellosis is the standard tube agglutination (STA) test. Although there is no clear diagnostic cutoff, a positive titer of >1/160 in non-endemic regions and >1/320 in endemic regions is generally used for diagnosis.[7] The Rose Bengal test is mostly used for screening purposes.

In this study, we aimed to retrospectively evaluate the demographic, laboratory, and clinical characteristics of pediatric brucellosis cases in the pre and post-COVID-19 era.

MATERIAL AND METHODS

Between April 1, 2019, and April 1, 2021, all children under 18 years of age diagnosed with brucellosis at our secondary care hospital were retrospectively screened. In our clinic, the Rose Bengal screening test is routinely performed during the initial screening for brucellosis within an appropriate clinical context. The diagnosis of brucellosis is confirmed in patients with clinical findings compatible with the disease and positive results in both the Rose Bengal and the STA test at a titer of >1/320. A dilution test was requested from the microbiology laboratory to address the prozone phenomenon in cases of strong clinical suspicion and negative STA.[8] Patients whose tests turned positive after dilution were included in our cohort. Due to logistical challenges, blood culture was not always available.

After the announcement of the first COVID-19 case in Türkiye in March 2020, all patients presenting with typical brucellosis symptoms such as fever, myalgia, and arthralgia were also screened for COVID-19 in our clinic. Real-time polymerase chain reaction (RT-PCR) tests were performed using nasopharyngeal specimens on a CFX96 real-time PCR device (Bio-Rad, USA) in the province central laboratory. The single nasopharyngeal swab has a 77% sensitivity for detecting COVID-19 infection.[9] Patients with suspected brucellosis requiring hospital admission after March 2020 were initially placed in isolation rooms with COVID-19 precautions until a negative PCR result was obtained. Outpatients were advised to follow isolation guidelines in their daily lives until the COVID-19 test result was received.

Clinical, laboratory, and demographic data of the patients were retrieved from electronic medical records. Approval for the study was granted by the local ethics committee. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Categorical variables are presented as numbers (percentages), while continuous variables are expressed as either median (interquartile range, IQR) or mean±standard deviation, depending on their distribution. Distribution was assessed both visually with histograms and statistically with skewness and kurtosis tests. The variance of normally distributed variables was determined using the Levene test. For bivariate analysis of categorical variables, the Chi-square test or Fisher's Exact test was employed as appropriate. The two-sample t-test was used for bivariate analysis with continuous independent variables and dichotomous dependent variables, provided the test assumptions were met. For continuous independent variables where assumptions were not met, the non-parametric alternative, the Mann-Whitney U test, was utilized. A p-value ≤.05 was considered statistically significant. Statistical analyses were conducted using STATA software, version 17.0 (StataCorp LLC, College Station, TX-USA).

RESULTS

Demographics

During the study period, a total of 71 patients had a positive Rose Bengal test. Out of these, 59 were confirmed with the STA test, establishing a diagnosis of brucellosis in 59 children over two years. There was a male predominance in our study population, with 64.4% (n=38) of the patients being male, and the median age was 11 years (range 5-16). The majority of cases were diagnosed in the spring and summer months, accounting for 40.7% and 35.6% of cases, respectively. Eight patients (13.6%) had a family member recently diagnosed with brucellosis. All patients had either consumed unpasteurized dairy products or had close contact with sheep or goats (Table 1).

Clinical Findings

The most common reasons for presentation were arthralgia and fever, 81.4% and 37.3%, respectively. Nearly two-thirds of the patients were afebrile at presentation. Other symptoms included chills, myalgia, fatigue, headache, abdominal pain, vomiting, and weight loss. Although arthralgia was the most prevalent symptom, arthritis was only observed in five patients (8.5%). Among the 48 patients presenting with arthralgia, the knee was the most commonly affected single joint (23.7%), followed by the sacroiliac joint (18.6%) and hip (13.6%). Ten patients (16.9%) experienced polyarthralgia.

Table 1: General characteristics of study population

n=59	
Age, year, median (IQR)	11 (6–15)
Gender, male, n (%)	38 (64.4)
Family history, n (%)	8 (13.6)
Relapse, n (%)	8 (13.6)
Hospital admission, n (%)	12 (20.3)
Season, n (%)	
Spring	24 (40.7)
Summer	21 (35.6)
Autumn	6 (10.2)
Winter	8 (13.6)
Symptoms, n (%)	
Fever	22 (37.3)
Arthralgia	48 (81.4)
Myalgia	13 (22)
Fatigue	15 (25.4)
Joint, n (%)	
Knee	14 (23.7)
Hip	8 (13.6)
Iliosacral	11 (18.6)
Elbow	3 (5.1)
Ankle	2 (3.4)
Polyarticular	10 (16.9)
Blood culture, n (%)	
Brucella sp. growth	9 (15.3)
No growth	12 (20.3)
Not obtained	38 (64.4)
STA, median (IQR)	2560 (640–5120)
CRP, mg/dL, median (IQR)	1.0 (0.5–2.1)
ESR, mm/h, median (IQR)	18.5 (9–32)
Leukocyte x10^9/L, median (IQR)	7.0 (5.9–8.3)
Neutrophil x10^9/L, median (IQR)	3.1 (2.3–3.9)
Lymphocyte x10^9/L, median (IQR)	3.0 (2.4–3.9)
Hemoglobin, g/dL, mean±SD	12.4±1.6
Thrombocyte x10^9/L, median (IQR)	262.4±73.4
AST, IU/L, median (IQR)	40 (31–51)
ALT, IU/L, median (IQR)	35 (24–48)
LDH, IU/L, median (IQR)	307 (240–429)

STA: Standard tube agglutination; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; AST: Aspartate transaminase; ALT: Alanine transaminase; LDH: Lactate dehydrogenase; IQR: Interquartile range; SD: Standard deviation.

Laboratory and Hematologic Findings

Blood culture was obtained from 21 (35.6%) patients, and nine were positive (42.9%). The median STA titration at the time of diagnosis was 2560 (range 640-5120). The most commonly identified hematological abnormality in patients was anemia (n=20), followed by lymphopenia (n=3), thrombocytopenia (n=3), leukocytosis (n=2), and neutropenia (n=1). Other common laboratory abnormalities in children with brucellosis included increased C-reactive protein (CRP) (>1 mg/dL) in 50.8% of patients, increased erythrocyte sedimentation rate (>20 mm/hour) in 46.5% of patients, elevated aminotransferases (>40 u/L) in 55.2% of patients, and elevated lactate dehydrogenase (>250 u/L) in 55.9% of patients (Table 1).

Most of the patients (79.7%) initiated and completed their treatment in an outpatient setting. Twelve (20.3%) patients required hospital admission for brucellosis treatment (Table 1). Although none of the patients presented after March 2020 had a positive COVID-19 PCR test, all were screened for COVID-19, and isolation precautions were implemented.

Patients presenting with fever were younger and had a higher proportion of elevated CRP and lower hemoglobin levels than afebrile patients, with the differences being statistically significant (p=0.01 for all comparisons). Febrile patients were more likely to present in the spring-summer months, and the need for hospital admission was higher in febrile patients than in afebrile patients (p=0.001 and p<0.001, respectively). Bacteremic patients had a higher ratio of hospital admission, elevated CRP, and lower hemoglobin levels compared to non-bacteremic patients, with the differences being statistically significant (p<0.001, p=0.02, and p=0.01, respectively). The percentage of elevated CRP was higher in admitted children than in non-admitted children (p=0.001), and complete bivariate comparisons are shown in Tables 2–4.

DISCUSSION

COVID-19 and brucellosis share many common presenting symptoms and laboratory findings. Fever could be the only or one of the presenting symptoms in both COVID-19 and brucellosis, as with many other infections. However, these two distinct infections, one bacterial and one viral, have other common features in their presentation. In our study, 81.4% of children with brucellosis presented with arthralgia, and 22% with myalgia, while musculoskeletal complaints have been reported as part of COVID-19 symptomatology in up to 90% of patients.[10] Anemia, leukopenia, and thrombocytopenia are known hematological manifestations of both brucellosis and COVID-19.[11,12] The most common cytopenia at the time of brucellosis diagnosis in our study was anemia (33.9%), followed by thrombocytopenia (5.1%), lymphopenia (5.1%), and neutropenia (0.2%).

Several case reports have been published presenting brucellosis cases that mimic COVID-19.[13–15] Moreover, patients co-infected with COVID-19 and *Brucella* have also been reported in the literatüre.[16,17]

Table 2: Bivariate comparison based on fever status

	Febrile (n=22)	Afebrile (n=37)	p
Clinical characteristics			
Age, year, n (%)	7 (4–12)	12 (8–15)	0.01
Gender, male, n (%)	11 (50)	27 (73)	0.07
Season, n (%)			0.001
Spring-Summer	22 (100)	23 (62.2)	
Autumn-Winter	0 (0)	14 (37.8)	
Hospital admission, n (%)	10 (45.5)	2 (5.4)	<0.001
Laboratory and hematological findings			
STA, median (IQR)	2560 (640–5120)	1280 (640–5120)	0.9
CRP, >1 mg/dL, n (%)	16 (72.7)	14 (37.8)	0.01
Leukocyte x10^9/L, median (IQR)	6.7 (5.5–8.3)	7.3 (6.4–8.4)	0.3
Neutrophil x10^9/L, median (IQR)	2.9 (2.3–3.7)	3.2 (2.6–4.0)	0.3
Lymphocyte x10^9/L, median (IQR)	3.0 (2.2–3.9)	3.1 (2.4–3.8)	0.9
Thrombocyte x10^9/L, median (IQR)	240 (193–277)	259.5 (218.5–283.0)	0.6
Hemoglobin, g/dL, mean±SD	11.7±1.8	12.7±1.3	0.01
AST, IU/L, median (IQR)	42 (35–59)	39 (27–48)	0.1
ALT, IU/L, median (IQR)	37.8 (24–45)	33 (24–48)	0.3
Blood culture positivity, n (%)	5 (38.5)	4 (50)	0.6

STA: Standard tube agglutination; CRP: C-reactive protein; AST: Aspartate transaminase; ALT: Alanine transaminase; IQR: Interquartile range; SD: Standard deviation.

Table 3: Bivariate comparison based on bacteremia status

	Bacteremic (n=9)	Non-bacteremic (n=12)	p
Clinical characteristics			
Age, year, median (IQR)	10.8±4.5	9.7±5.6	0.6
Gender, male, n (%)	6 (66.7)	8 (66.7)	1.0
Season, n (%)			0.7
Spring-Summer	7 (77.8)	8 (66.7)	
Autumn-Winter	2 (22.2)	4 (33.3)	
Hospital admission, n (%)	10 (45.5)	2 (5.4)	<0.001
Laboratory and hematological findings			
STA, median (IQR)	5120 (1280–5120)	2560 (640–5120)	0.8
CRP, >1 mg/dL, n (%)	8 (88.9)	4 (33.3)	0.02
Leukocyte x10^9/L, median (IQR)	6.7 (5.6–6.9)	7.1 (6.2–7.8)	0.3
Neutrophil x10^9/L, median (IQR)	2.7 (2.4–3.2)	3.8 (2.5–4.5)	0.1
Lymphocyte x10^9/L, median (IQR)	2.9 (2.4–3.5)	2.9 (2.4–3.8)	1.0
Thrombocyte x10^9/L, median (IQR)	260 (183–279)	250 (220–296)	0.9
Hemoglobin, g/dL, mean±SD	11.7±1.8	12.7±1.3	0.01
AST, IU/L, median (IQR)	42 (35–59)	39 (27–48)	0.1
ALT, IU/L, median (IQR)	37.8 (24–45)	33 (24–48)	0.3

STA: Standard tube agglutination; CRP: C-reactive protein; AST: Aspartate transaminase; ALT: Alanine transaminase; IQR: Interquartile range; SD: Standard deviation.

Table 4: Bivariate comparison based on hospital admission status

	Admitted (n=12)	Not admitted (n=47)	p
Clinical characteristics			
Age, year, median (IQR)	8.5 (4.5–15)	11 (6–15)	0.5
Gender, male, n (%)	6 (50.0)	32 (68.1)	0.2
Season, n (%)			0.05
Spring-Summer	12 (100.0)	33 (70.2)	
Autumn-Winter	0 (0.0)	14 (29.8)	
Hospital admission, n (%)			
Laboratory and hematological findings			
STA, median (IQR)	2560 (320–5120)	1280 (640–5120)	0.7
CRP, >1 mg/dL, n (%)	10 (83.3)	20 (42.6)	0.001
Leukocyte x10^9/L, median (IQR)	5.6 (5.3–9.8)	7.4 (6.4–8.3)	0.06
Neutrophil x10^9/L, median (IQR)	2.6 (2.0–5.8)	3.2 (2.6–3.9)	0.5
Lymphocyte x10^9/L, median (IQR)	2.7 (2.0–3.4)	3.3 (2.6–4.0)	0.1
Thrombocyte x10^9/L, median (IQR)	265 (250–344)	258 (210–280)	0.2
Hemoglobin, g/dL, mean±SD	11.5±1.7	12.0±3.0	0.6
AST, IU/L, median (IQR)	42 (31–52)	40 (31–49)	0.7
ALT, IU/L, median (IQR)	36 (18–45)	34 (24–48)	0.8
Blood culture positivity, n (%)	4 (66.7)	5 (33.3)	0.3

STA: Standard tube agglutination; CRP: C-reactive protein; AST: Aspartate transaminase; ALT: Alanine transaminase; IQR: Interquartile range; SD: Standard deviation.

Although our patient cohort did not have any co-infections, all patients diagnosed with brucellosis who presented after March 2020 were screened for COVID-19 and remained in isolation until negative COVID-19 test results were received, due to the similarity in symptomatology. However, it is possible that some cases may have been missed, given that the sensitivity of a single nasopharyngeal swab PCR test is 77%.[9]

Arthralgia was the most common presenting symptom in our patient population, with more than half of the patients being afebrile. Contrary to our findings, fever is generally reported as the most common presenting symptom in the literature; however, the percentages of symptoms vary significantly between studies.[18–20] Similar to our results, Sarı et al.[21] reported in a single-center study from the Van province of eastern Türkiye that 48% of 43 pediatric patients diagnosed with brucellosis presented with fever, whereas 72% had arthralgia. Geographic distribution may influence symptomatology, though this remains speculative. Another potential explanation for the high proportion of afebrile patients in our cohort is brucellosis's characteristic undulant, wave-like nature of fever.[22] Despite taking detailed histories from patients and caregivers in cases of suspected or confirmed brucellosis, they might not have reported a history of fever due to its fluctuating nature. Nonetheless, healthcare providers should maintain a high degree of suspicion for brucellosis in patients presenting with musculoskeletal complaints without fever, especially in endemic areas or in those with epidemiological exposure in non-endemic regions.

The blood culture positivity rate for *Brucella* species in our patient population was 42.9%, with elevated CRP ratios being higher in the bacteremic group. Gaifer et al.[23] from Saudi Arabia recently reported a 42% blood culture positivity rate in 147 brucellosis cases, predominantly among adults. Ma et al.[20] from China found a 65% blood culture positivity rate and a 53% elevated CRP rate in children with brucellosis. In one pediatric brucellosis study, the blood culture positivity rate was 28%, with increased acute phase reactants and higher STA values identified as predictive parameters for positive blood culture.[24] Another pediatric study from Türkiye reported a 34% blood culture positivity rate, with higher percentages of hepatomegaly, splenomegaly, fever presence, and CRP and liver enzyme values in the bacteremic group.[25] Although blood cultures were not obtained from some patients in our cohort, our blood culture positivity and elevated CRP rates align with recent literature.

Our study has several limitations: its retrospective, single-center design restricts causal inferences from our results. The absence of blood culture data for some patients diminishes this variable's significance in the study. Larger multicenter studies are required to better understand pediatric brucellosis's public health implications and the impact of the COVID-19 pandemic on the diagnosis and treatment of brucellosis.

CONCLUSION

The symptoms of COVID-19 and brucellosis in children overlap, making the diagnosis of brucellosis particularly challenging, especially in areas with low prevalence. It is crucial not to overlook a brucellosis diagnosis in afebrile patients, as evidenced by the high percentage of afebrile children diagnosed with brucellosis in our study. CRP levels may serve as a useful predictor for the presence of bacteremia and the necessity for hospital admission.

Statement

Ethics Committee Approval: The Siirt University Clinical Research Ethics Committee granted approval for this study (date: 30.04.2021, number: 8735).

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

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