Osteoarticular Involvement in Childhood Brucellosis: Evaluation of Clinical, Laboratory and Radiologic Features of 185 Cases

Gulsen Akkoc, MD,† and Serhat Tekerek, MD‡§*

Backgrounds: Brucellosis is a systemic zoonotic disease. Osteoarticular (OA) system involvement is a common complication and the predominant manifestation of brucellosis in children. We aimed to evaluate the epidemiologic, demographic, clinical characteristics, and laboratory and radiologic findings of children with brucellosis and how these related to OA involvement.

Methods: This retrospective cohort study consisted of all consecutive children and adolescents diagnosed as having brucellosis who were admitted to the pediatric infectious disease department of University of Health Sciences Van Research and Training Hospital between August 1, 2017, and December 31, 2018, in Turkey.

Results: A total of 185 patients diagnosed as having brucellosis were evaluated, 50.8% had OA involvement (n = 94). Seventy-two patients (76.6%) exhibited peripheral arthritis involvement, among of them, hip arthritis (63.9%; n = 46) was the most common manifestation, followed by arthritis of knee (30.6%; n = 22), shoulder (4.2%; n = 3) and elbow (4.2%; n = 3). A total of 31 patients (33.0%) had sacroiliac joint involvement. Seven patients (7.4%) had spinal brucellosis. Erythrocyte sedimentation rate level above 20 mm/h at admission and age were independent predictor of OA involvement (respectively odds ratio [OR] = 2.82; 95% confidential interval [CI] = 1.41–5.64, $OR_{peryear}$ = 1.10; 95% CI: 1.01–1.19). Increasing age was associated types of OA involvement.

Conclusion: A half of brucellosis cases had OA involvement. These results can help physicians to make early identification and diagnosis of childhood OA brucellosis who present with arthritis and arthralgia to enable the disease to be treated in time.

Key Words: Arthritis, Brucellosis, children, osteoarticular involvement, radiology

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Brucellosis is a systemic zoonotic disease that occurs worldwide but predominantly in endemic regions (the Mediterranean basin, the Arabian Peninsula, the Indian subcontinent, and parts of Mexico, Central America, and South America).[1] *Brucella* species are transmitted to people, such as farmers, shepherds, abattoir workers and veterinarians, through direct contact with infected animals or carcasses. A large number of cases of the disease involve family clusters stemming from infection through consumption of dairy products, primarily unpasteurized milk, obtained from infected animals.[1,2] Children account for approximately 10%–30% of all brucellosis cases.[3–7]

Brucellosis can infect any organ or system. It is generally characterized by nonspecific complaints (fever, malaise, sweating) and abnormal physical findings (ie, hepatomegaly or splenomegaly).[2,6–10] Prominent localized signs and symptoms are a consequence of the involvement of particular organs or systems such as the skeletal (osteoarticular; OA) system, nervous system or heart.[9–11] OA involvement is a common complication and the predominant manifestation of brucellosis in children, appearing in 10%–85% of cases involving children.[9–15] In contrast to adult brucellosis, in which sacroiliac involvement is common, arthritis of the large peripheral joints (knee, hip, ankles) is more common in childhood brucellosis.[2,9,10,12–14,16,17] Sacroiliitis and spondylitis are rare in childhood brucellosis.[2,9,10,16,17]

It is not currently understood why OA involvement is relatively common in children. Most research has focused only on a small number of children with OA brucellosis, and reports of the frequency of OA complications and their specific sites of involvement have varied in these studies.[2,4,6,9,10,12,14,17–19] The variation in reported frequencies may be because of local or age-related differences, which appear to play a role in the incidence, pattern and presentation of OA brucellosis in children.[1,2,9,13,17,20]

The primary objective of this study was to evaluate the epidemiologic, demographic, and clinical characteristics, and laboratory and radiologic findings of children with brucellosis who presented to our pediatric infectious diseases department. The secondary objectives were to determine the frequency and types of OA involvement and the predictors of OA involvement in childhood brucellosis.

MATERIALS AND METHODS

The study protocol accorded with the Helsinki Declaration. Ethical approval to conduct this study was obtained from the Institutional Review Board of Health Ministry University Van Research and Training Hospital (Number: 2019/06). Written consent was obtained from the parents of enrolled children.

Setting and Patients

The population for this retrospective cohort study consisted of all consecutive children and adolescents diagnosed with brucellosis who were admitted to the pediatric infectious disease outpatient and inpatient clinics of Health Ministry University Van Research and Training Hospital between August 1, 2017, and December 31, 2018, in Turkey. In total, 210 patients were enrolled in the study.

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From the *Department of Pediatric Infectious Disease, University of Health Sciences Van Research and Training Hospital Van, Van, Turkey; †Department of Pediatric Infectious Disease, University of Health Sciences, Haseki Training and Research Hospital Istanbul, Istanbul, Turkey; ‡Department of Radiology, University of Health Sciences Van Research and Training Hospital Van, Van, Turkey; and §Department of Radiology, University of Health Sciences Antalya Research and Training Hospital Antalya, Antalya, Turkey.

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G.A. conceived and designed the study, contributed to the acquisition, analysis and interpretation of data, and drafted the article. S.K. performed ultrasonography, analyzed MRI findings, contributed to the analysis and interpretation of the data, and approved the final version for publication.

Informed consent was obtained from the parents of the patients.

Address for correspondence: Gulsen Akkoc, MD, Division of Pediatric Infectious Diseases, Department of Pediatrics, Marmara University School of Medicine, Fevzi Cakmak mahallesi No:41 Ustkaynarca/Pendik/ISTANBUL, 34890 Istanbul, Turkey. E-mail: agulsenakkoc@gmail.com.

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Diagnostic Criteria

The diagnosis of brucellosis was made on the basis of clinical features consistent with the illness, epidemiological features, and one of the following laboratory criteria: either the isolation of a *Brucella* species from a blood sample or synovial fluid or the identification of specific antibodies at significant titers. Significant titers were defined as a seroagglutination test (STA) result of ≥1/160 and a Coombs anti-*Brucella* agglutination test result of ≥1/160.

Study Design and Group Definitions

The data set was divided into 2 groups according to OA involvement. The OA+ group was defined as having signs and symptoms of arthritis and evidence of arthritis based on imaging studies. The OA− group was defined as having systemic brucellosis without signs and symptoms of arthritis or evidence of arthritis based on imaging studies. Patients with symptoms but without evidence of arthritis based on imaging studies were defined as uncategorized (n = 25), and this population was excluded from the comparison of the OA+ (n = 94) and OA− (n = 91) groups, for which a total of 185 patients were evaluated.

Data Collection

Demographic features, epidemiologic history, clinical data, and laboratory and imaging (ultrasonography [USG] and magnetic resonance imaging [MRI]) findings upon admission were recorded retrospectively. Cases with a preliminary diagnosis of brucellosis were routinely tested to determine complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and biochemical function. Radiologic studies were performed in all cases of diagnosed or suspected arthritis.

Types of OA involvement, treatment protocols, and methods of laboratory and radiologic studies were summarized in Supplemental Digital Content 1 http://links.lww.com/INF/E929 (Material and Methods).

The demographic, clinical and laboratory characteristics were compared between the 2 groups. For the secondary objectives of the study, the types of OA involvement were determined as well as the frequency thereof, and predictors of OA involvement in childhood brucellosis were identified.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 (IBM Corp, Armonk, NY, United States). The Shapiro-Wilk test was used to determine whether the variables were normally distributed. Numbers and percentages were used to express categorical variables. The mean ± standard deviation or the median with the interquartile range (IQR) was used to express continuous variables depending on whether they exhibited a parametric or nonparametric distribution. Categorical variables were compared using the chi-square test. The Mann-Whitney *U* test and Student's *t* test were used to compare median or mean values between the 2 groups, depending on the sample distribution. A *P* value of less than 0.05 was used as the cutoff for statistical significance. For the multivariate analysis, the possible factors identified through univariate analysis were entered into a logistic regression analysis to determine independent predictors of OA involvement. Variables that demonstrated a significant univariate relationship between OA groups in the sample group without collinearity were included in a logistic regression model to determine the independent predictors of OA involvement. The ability of ESR level to predict OA involvement was analyzed using receiver operating characteristic (ROC) curve analysis. For each parameter, sensitivity and specificity and area under the ROC curve (AUC) were calculated as diagnostic tools for predicting OA involvement. When evaluating the AUC, a 5% type-I error rate was used to define a statistically significant predictive value.

RESULTS

Demographics and Clinical and Laboratory Findings of Brucellosis Cases

A total of 185 patients diagnosed as having brucellosis were evaluated. One hundred fourteen (61.6%) were boys, and the mean age was 136 ± 51.6 months. One hundred eighty two patients (98.4%) had a positive STA result, and 80.5% of patients had detectable Brucella spp. was identified in their blood cultures (n=149) at admission. Moreover, *Brucella* spp. was yielded in both blood and knee synovial aspirate cultures of 4 patients. All patients with negative STA test results had positive blood culture results. The mean leukocyte count was 7388 ± 2542 cells/mm^3, and the median CRP, ESR, alanine aminotransferase and aspartate aminotransferase levels were 12.2 mg/dL (IQR: 5.41–21.95 mg/dL), 28 mm/h (IQR: 14–40 mm/h), 26 IU/L (IQR: 18–45 IU/L), and 35 IU/L (IQR: 25–49 IU/L).

OA+ group

Ninety four patients (50.8%) had OA involvement. The demographic and epidemiologic characteristics of the OA+ group are shown in Table 1. The most common symptom in the OA+ group was arthralgia (100%) followed by, in order, myalgia (64.9%), fever (58.5%), and fatigue (8.5%). Splenomegaly was observed in 2 patients and hepatomegaly in 1 patient. The laboratory results of the OA+ group are summarized in Table 1. For radiologic imaging, OA involvement was diagnosed using MRI or USG in 81 (86.2%) and 13 patients (13.8%), respectively. Seventy-five patients in the OA+ group (79.8%) received rifampicin plus doxycycline or trimethoprim/sulfamethoxazole plus gentamicin or streptomycin therapy, and 16 (17.0%) received rifampicin plus doxycycline or trimethoprim/sulfamethoxazole. Three patients experienced drug allergies and so, with their parents' consent, were administered ciprofloxacin therapy. All hospitalized patients were discharged with a good outcome. Three patients (3.3%) had relapses. Seventy (74.4%) patients in the OA+ group received treatment lasting ≥12 weeks, with the rest receiving treatment for 6 weeks. The types and localizations of all OA involvements are shown Figure 1.

Peripheral Arthritis

Seventy-two patients (76.6%) exhibited peripheral arthritis, 46 (63.9%) of whom were boys. The mean age of this group was 137 ± 50.4 months. Radiologic diagnosis of peripheral arthritis was mostly performed using MRI (81.9%) rather than USG (18.1%). Hip arthritis (63.9%; n = 46) was the most common manifestation, followed by arthritis of the knee (30.6%; n = 22), shoulder (4.2%; n = 3), elbow (4.2%; n = 3) and ankle (1.1%; n = 1). In the peripheral arthritis group, 95.7% of patients had arthritis in only 1 joint type with 50 (72.4%) patients having unilateral involvement. Three patients had involvement of 2 different peripheral joints. The radiologic findings from patients with peripheral joint involvement are shown in Tables 2 and 3.

Sacroiliitis

A total of 31 patients had sacroiliac joint involvement, eighteen (58.1%) of which were girls. This group had a mean age of 169 ± 31.6 months. Multiple involvement was observed in 45.2% of these patients. MRI was used to identify all inflammatory changes in all patients. The radiologic findings are shown in Table 2.

TABLE 1. Comparison of OA (+) and OA (−) Patient Groups on Demographic, Epidemiologic and Laboratory Findings

		OA+ [n = 94]	OA− [n = 91]	*P**
Demographic features				
Gender n, (%)				
	Girl	39 (41.5)	32 (35.2)	0.377
	Boy	55 (58.5)	59 (64.8)	
Age, months		144 ± 49.59	126 ± 52.96	**0.018**
Age groups n, (%)	<5 years old	6 (6.4)	13 (14.3)	0.083
	≥5–<10 years old	18 (19.1)	26 (28.6)	
	≥10–<15 years old	48 (51.1)	35 (38.5)	
	≥15 years old	22 (23.4)	17 (18.7)	
Exposure history n, (%)				
Consumption of unpasteurized dairy products		93 (98.9)	90 (98.9)	1
Contact with animal or secretions		43 (45.7)	37 (40.7)	0.485
Seasonal distribution (August 1, 2017–December 31, 2017; n = 64) n, (%)				
Spring		–	–	0.276
Summer		5 (13.5)	2 (7.4)	
Autumn		25 (67.6)	20 (74.1)	
Winter		7 (18.9)	5 (18.5)	
Seasonal Distribution (year:2018; n = 121) n, (%)				
Spring		6 (10.5)	9 (14.1)	0.502
Summer		17 (29.8)	18 (28.1)	
Autumn		19 (33.3)	26 (40.6)	
Winter		15 (26.4)	11 (17.2)	
Laboratory findings				
STA at admission, n (%)				
	Negative	0 (0)	1 (1.1)	
	1/80	1 (1.1)	1 (1.1)	
	1/160	2 (2.1)	1 (1.1)	
	1/320	6 (6.4)	10 (11.0)	
	1/640	15 (16.0)	18 (19.8)	
	1/1280	29 (30.9)	22 (24.2)	
	1/2560	18 (19.1)	11 (12.1)	
	≥1/5120	23 (24.5)	27 (29.7)	
Culture positivity, n (%)		60 (63.8)	89 (97.8)	**<0.001**
Leukocyte,/mm^3		8133 ± 2235	6745 ± 2632	**0.004**
Leukocytosis (%)		13.7	1.7	**0.024**
Leukopenia		2.0	8.5	0.213
Platelet,/mm^3		306.275 ± 82.538	253.483 ± 95.959	**0.003**
CRP, mg/dL		14.5 (5.82; 28.15)	10 (5.4; 19)	**0.043**
CRP>10 (%)		66.3	50.7	**0.045**
ESR, mm /h		33 (18.25; 44)	20.5 (12; 35)	**0.001**
ESR>20 (%)		73.8	51.3	**0.003**
ALT, IU/L		22 (16; 30)	32 (22; 71.2)	**<0.001**
AST, IU/L		27 (21; 40)	45 (31; 65.45)	**<0.001**

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; STA, seroagglutination test.
Significant *P* values (<0.05) were represented with bold.
*Chi-square test. The Mann-Whitney *U* test and Student's *t* test were used depend on variables.

Spinal Brucellosis

Seven patients, predominantly boys (85.7%), had spinal brucellosis. The mean age of this group was 181 ± 24.5 months. MRI was used to identify all inflammatory changes in all patients. The radiologic findings are shown in Table 2.

OA− Group

A total of 91 patients were evaluated in the OA− group. The demographic and epidemiologic characteristics of the OA− group are shown in Table 1. The most common symptom in the OA− group was fever (74.7%), followed by, in order, myalgia (64.8%), fatigue (11.0%), headache (4.4%), and sweating (3.3%). Common signs in the OA− group were splenomegaly (17.6%; n = 16) and hepatomegaly (6.6%; n = 6). The laboratory results of the OA− group are summarized in Table 1. Fifty-six (61.5%) of the OA− group received rifampicin plus doxycycline or trimethoprim/sulfamethoxazole plus gentamicin or streptomycin therapy, and 32 (35.2%) received rifampicin plus doxycycline or trimethoprim/sulfamethoxazole. Three patients experienced drug allergies and so, with their parents' consent, were administered ciprofloxacin therapy. All hospitalized patients were discharged with a good outcome. Fifty-nine (64.8%) of the OA− group received treatment for 6 weeks. Four (4.4%) patients had relapses.

Comparison of the Demographics and Laboratory Findings According to OA Involvement and Identification of Predictors for OA Involvement

The mean age of the OA− group was lower than that of the OA+ group ($P = 0.018$). The hospitalization ratio significantly differed between the OA+ and OA− groups: 80.9% (76 patients) versus 16.5% (15 patients), $P < 0.001$. The mean leukocyte and platelet counts and the mean CRP and ESR levels were significantly higher ($P = 0.004$, $P = 0.003$, $P = 0.043$, and $P = 0.001$), and the mean ALT and AST levels were significantly lower ($P \leq 0.001$ for each) in the OA+ group compared with the OA− group (Table 1).

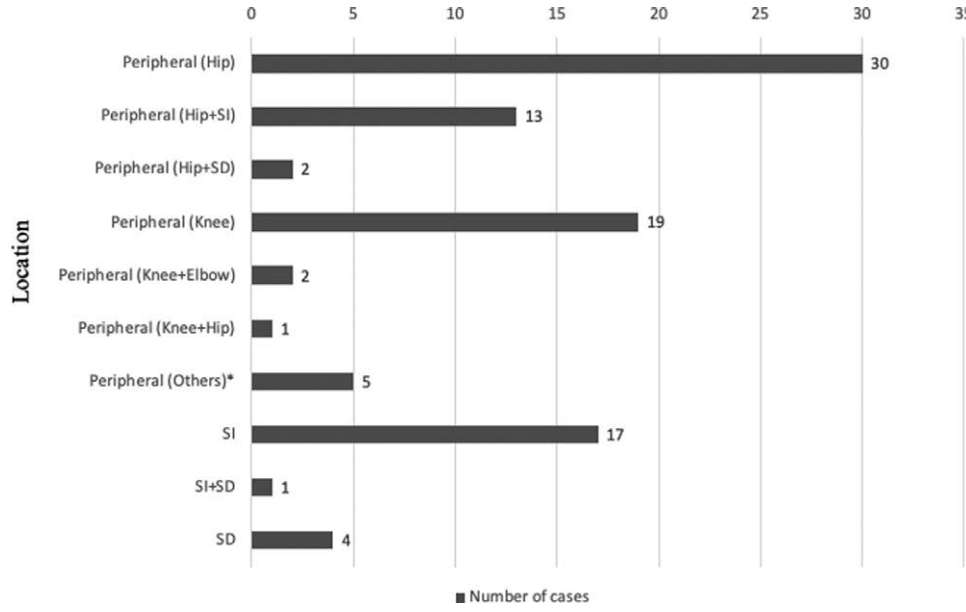

FIGURE 1. The distribution of osteoarticular involvement according to location. Some patients had multiple involvement location. Peripheral joint involvement: 72 patients (hip:46, knee:22, shoulder:3, elbow:3, ankle 1 patient); sacroiliitis: 31 patients (13 patients with hip, 1 patient with spondylitis); spondylitis: 7 patients (2 patients with hip, 1 patient with sacroiliitis). *Others: 5 patients (shoulder: 3, elbow: 1, ankle: 1 patients). SD indicates spondylitis; SI, sacroiliitis.

For predicting OA involvement, a multivariate logistic regression model, which was based on demographic features, age, ESR level above 20 mm/h, and CRP level above 10 mg/dL, revealed that an ESR level above 20 mm/h at admission and age were independent predictors of OA involvement with odds ratios of 2.82 (95% confidential interval [CI]: 1.41–5.64) and 1.10 per year (95% CI: 1.01–1.19). The diagnostic cutoff of an ESR of 24 mm/h had a sensitivity of 60.9 and specificity of 60.3 for predicting OA involvement (AUC of ESR = 0.666; 95% CI: 0.576–0.745; P = 0.001; Fig. 2).

DISCUSSION

We evaluated the demographic and clinical characteristics and laboratory and radiologic features of patients diagnosed with brucellosis. In our study group, a relatively large number of children had brucellosis (n = 185). Thus, this cohort provided an opportunity to prepare a well-rounded report on the descriptive, clinical and laboratory characteristics and detailed description of radiologic features of childhood brucellosis.

One-third of patients in this study were aged between 10 and 15 years. In childhood brucellosis cohort studies, the majority of cases have generally been older children.[6,17–19] Although children of all ages are susceptible to brucellosis, our sample properly reflected the age distribution of childhood brucellosis.[6,7] In our cohort, boys were more frequently diagnosed with brucellosis than girls. This is consistent with literature reports of boys comprising 55%–79% of childhood brucellosis cases.[2,6,10,17,20,21] The prevalence of brucellosis and the transmission from animals to humans depends on several factors, such as country of residence, cultural practices (eg, traditional husbandry practices or consumption of unpasteurized dairy products), and the characteristics of the causative pathogen.[1,2,9,17,20] Consequently, differences may be evident in the demographic data reported from different regions because of such local differences.

The frequency of OA involvement in the present study was 50.8%. OA involvement is the most common complication in children; however, studies show a wide range of incidence of 6%–56%.[4,6,9,14,15,19,22] We found that two-thirds of the OA+ group had peripheral arthritis, with sacroiliitis and spondylitis the next most common types of OA involvement. This result accords with the literature suggesting that peripheral arthritis is seen more frequently in children than adults, with a range of 13%–71%.[9,14,23] Additionally, the localization of OA involvement mainly depends on the age of the patient, and it has been observed that peripheral arthritis is the major presentation in children but not adults.[9,14,23–28] Various studies have reported that either the hip or the knee joint is the most prevalent site of peripheral OA involvement. In our cohort, the hip was the most common site of peripheral involvement.[10,12,13,17,19–21,24,26] Monoarthritis is common in children, accounting for 80%–90% of joint involvement, and our results accord with the literature.[12,13,19,21,23] The unilateral involvement observed in the majority of peripheral arthritis cases in our study, however, contrasts with the literature, where bilateral involvement has been observed with notable frequency.[9,17,24] The possible reason for the high incidence of involvement of the peripheral joints such as the hips and knees may be that the synovial membranes of these joints facilitate the entry of bacteria into the joint space during bacteremia because of the high density of the vascular connective tissue layer and the absence of a basement membrane.[29,30] In this study, we reported the involvement of other small joints (shoulder, elbow and ankle) close to the 3%–13% range reported in the literature.[9,13,14,17,19,21,24,25,31–33] In addition, osteomyelitis and bursitis, which are rare in the literature, were observed in only a few cases alongside arthritis.[8,9,13,19,29,33–35]

In this current study, sacroiliitis was the second most second common OA presentation, with an incidence of 34%. Sacroiliitis is seen less commonly in children and has generally been reported at low frequencies (3.2–9.4%).[2,9,17,19,36,37] However, studies from the same area as ours have found high incidence, in the range of 48%–50%.[13,23,38] Unilateral involvement of the sacroiliac joint was observed in two-thirds of our patients. Sacroiliitis presents unilaterally in the majority of patients, with a range of 66%–84% reported in several studies focusing on children.[9,19,23,36–38] However, bilateral

TABLE 2. Radiologic Findings of the Patients Diagnosed Through Magnetic Resonance Imaging

Age	Gender	Patients With Sacroiliitis and Hip Arthritis												
		Coxofemoral (Hip) Joint									Sacroiliac Joint			
		UI	BI	EFF	SCE	ST	BME	LN	OM	OE	UI SI	BI SI	PE	SI Abscess
213	Boy										+			
210	Boy	+		+	+									
204	Boy	+		+	+						+			
204	Boy											+		
204	Girl										+			
203	Boy	+		+	+						+			
199	Boy		+	+	+									
198	Boy	+		+	+							+		
198	Girl										+			
195	Boy	+		+	+									
195	Boy										+			
194	Girl		+	+	+							+		
192	Boy	+		+	+	+								
192	Boy							+				+		
187	Boy							+			+			
187	Boy	+		+								+		
186	Girl										+			
178	Girl	+		+	+						+			
178	Girl											+		
176	Boy		+	+				+						
176	Girl										+			
176	Boy										+			
176	Boy	+		+	+									
175	Girl										+		+	+
173	Girl										+			+
171	Boy	+		+	+			+				+		
168	Boy	+		+			+							
168	Boy	+					+	+						
165	Girl		+	+	+							+		
165	Boy		+	+	+			+						
162	Boy		+	+	+									
159	Girl		+	+	+							+		
157	Girl							+				+		
154	Girl		+	+	+									
154	Girl	+		+								+		
153	Girl		+	+	+	+				+*				
153	Girl										+			
149	Girl	+		+	+			+						
148	Girl	+					+							
145	Boy		+	+	+		+							
145	Boy	+		+								+		
144	Boy	+		+	+									
141	Girl										+			
137	Boy		+	+	+		+							
136	Girl										+			
135	Boy		+	+	+	+								
126	Girl		+	+										
125	Girl										+			
114	Boy	+		+	+	+	+	+			+			
113	Girl		+	+	+									
101	Boy	+		+			+				+			
97	Girl	+		+	+	+	+							
90	Boy		+	+	+									
90	Girl	+		+	+	+								
86	Girl		+	+	+						+			
81	Girl	+		+										
71	Girl		+	+	+									
66	Girl	+		+	+			+						
66	Girl		+	+										
34	Boy	+		+	+			+						
23	Boy	+		+	+			+	+*					
17	Boy	+			+			+						
Number of patients	26/44	18/44	43/44	29/44	6/44	8/44	11/44	1/44	1/44	20/31	11/31	1/31	2/31	

(*Continued*)

TABLE 2. Radiologic Findings of the Patients Diagnosed Through Magnetic Resonance Imaging

Age	Gender												
		Patients with peripheral arthritis except hip											
		Site	UI	BI	EFF	SCE	ST	SE	Bursitis	OM	Myositis	LN	Tendinitis
181	Boy	Knee	+		+	+							
		Elbow	+		+								
179	Boy	Knee	+		+								
179	Boy	Knee	+		+	+							
178	Boy	Knee	+		+								
172	Boy	Knee	+		+			+					
165	Boy	Knee	+		+	+							
		Elbow	+		+								+‡
134	Boy	Knee	+		+								
130	Girl	Knee		+	+	+							
113	Boy	Knee	+		+								
83	Boy	Knee	+		+								
			9/10	1/10	10/10	4/10	2/10	5/10					
172	Girl	Shoulder	+			+	+		+				
153	Girl	Shoulder	+		+						+	+	
149	Boy	Shoulder	+		+	+	+				+		
97	Boy	Ankle	+		+	+							
59	Girl	Elbow	+		+	+	+			+†			
		Patients with spondylitis											
		VL	DI	FI	Discitis	PI	Abscess	PN CE	Collection	EI			
207	Boy	L2-3	+			+							
203	Boy	T12-L1	+							+			
		L4-5	+				+						
195	Boy	L2-3	+		+	+	+	+		+			
176	Boy	T8-9	+			+			+	+			
		L4-5		+					+				
175	Boy	L2-3	+										
173	Girl	L4-5	+		+								
135	Boy	L4-5	+					+					
			7/7	1/7	2/7	3/7	2/7	2/7	2/7	3/7			

* Femur

†Humerus

‡Biceps brachii.

BI indicates bilateral involvement; BME, bone marrow edema; CE, contrast enhancement; DI, diffuse involvement; EFF, effusion; EI, extra-vertebral involvement; FI, focal involvement; LN, lymph node; OE, osseous erosions; OM, osteomyelitis; PE, periarticular edema; PI, paraspinal involvement; PN CE, perineural contrast enhancement; SCE, synovial contrast enhancement; SE, soft tissue edema; SI, sacroiliitis; ST, synovial thickening; UI, unilateral involvement; VL, vertebra level.

involvement has been reported to be more common in some adult studies.[13,25,27,32,33] We observed that sacroiliitis occurred with either spondylitis or peripheral arthritis in almost half of the patients, and this result was higher than in the literature, which has reported a range of 10%–14%.[27,39] However, Bosilovski et al reported that half of patients with sacroiliitis had either spondylitis or peripheral arthritis.[24] In the current study, all sacroiliitis was diagnosed with MRI. MRI may be helpful for diagnosis, especially earlier in the course of the disease.[24,40,41]

In the current study, with only 7 patients (7.4%) presented with spinal brucellosis. Although, spinal brucellosis is reported as rarely or none in children,[9,10,12,14,17,19,36,37] Gur et al and Geyik et al reported spondylitis rates of 17.9% and 17%, respectively.[13,38] In adults, spinal brucellosis is the one of the most common OA presentations, with a range of 10%–60%, and it commonly manifests as spondylitis, spondylodiscitis, or discitis.[27,29,42–44] In our study, the most common inflammatory changes were located in the lumbar spine followed by the thoracic spine, which accords with the literature, which has reported ranges of 60%–83% and 8.3%–19%, respectively.[27,32,43–45] We observed spondylodiscitis in only 2 patients, and this was localized to lumbar segments; however, it has been reported at higher percentages (ranging from 6% to 85%).[24,27,32,42] In our study, 2 patients had noncontagious multisegment involvement at different levels of the spine, and this accords with the literature range of 3%–14%.[27,32,39,43–47] We also observed serious but rare complications of spinal brucellosis such as epidural abscess, which has been reported to occur in the range of 7.1%–30%.[13,24,27,32,42,48] MRI was used for diagnosis in all cases and is the most valuable method for disclosing spinal brucellosis and its complications as well as making a differential diagnosis.[13,27,39,40,46–48]

Notably, no axial involvement (spondylitis and sacroiliitis) was observed in children <15 years old, which accords with Zamani et al, who found no axial involvement in children <12 years old.[12] Moreover, in this current study, patients with spondylitis and sacroiliitis were older than patients with peripheral arthritis, in line with findings from other studies.[9,14,19,37] These results suggest that OA involvement localization depends on the age of the patient, in addition to factors mentioned above.[9,14,23–28] Brucellosis should be considered in older children with axial complaints in *Brucella*-endemic regions.

Studies have reported that OA involvement increases with age and that patients with OA involvement are older than those without OA involvement.[9,12,19] In this study, the median age of OA-involved patients was higher than that in the OA− group; increasing age was found to be an independent predictor for OA

TABLE 3. Radiologic Findings of the Patients With Peripheral Arthritis Diagnosed Through Ultrasonography

Age	Gender	Site	UI	BI	EFF	ST	SE
210	Boy	Knee	+		+		+
185	Boy	Knee	+		+		+
184	Boy	Knee	+		+	+	+
176	Boy	Knee	+		+		
151	Girl	Knee	+		+	+	+
151	Boy	Knee	+		+		
133	Girl	Knee	+		+		
100	Boy	Knee		+	+		
		Hip	+		+		
94	Boy	Knee	+		+		
75	Girl	Knee	+		+		
61	Boy	Knee	+		+	+	
36	Boy	Knee	+		+		
			11/12	1/12	12/12	3/3	4/4
30	Girl	Hip	+		+		
			2/2		2/2		

BI indicates bilateral Involvement; EFF, effusion; SE, soft tissue edema; ST, synovial thickening; UI, unilateral involvement.

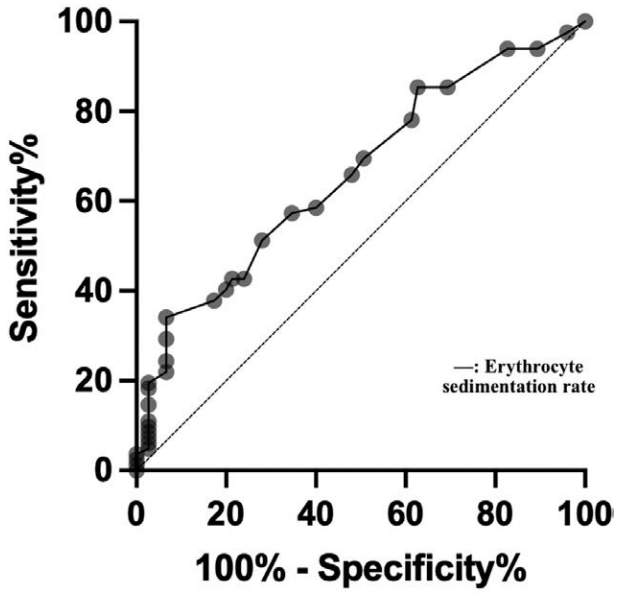

FIGURE 2. Comparison of specificity and sensitivity of ESR for osteoarticular involvement in patients with brucellosis, with ROC curve graph. ESR indicates erythrocyte sedimentation rate; ROC, receiving operation characteristic.

involvement. Guler et al determined that OA involvement was significantly associated with increasing age and that OA involvement was more frequent in adults than in children.[22] The significant relationship between age and OA involvement in this study indicates that OA involvement may be more common in older children with brucellosis. Therefore, radiologic imaging studies and close observation should be done promptly to prevent severe complications because of OA involvement in the presence of relevant complaints.

Brucellosis is diagnosed on the basis of a serological test or culture with clinical presentation.[2,6,20] Laboratory findings are commonly nonspecific but are useful as additional diagnostic methods.[2,6] We determined that elevated ESR was an independent predictor for OA involvement and a significant diagnostic criterion with high sensitivity and specificity for predicting OA involvement. Balın et al reported that ESR and CRP were useful parameters in predicting the clinical course of patients with brucellosis, especially for OA involvement, with high sensitivity and specificity of 70% and 60%, respectively, for ESR and 48% and 81%, respectively, for CRP.[49] Elevated ESR in brucellosis was closely related to OA involvement. These results suggest that ESR is a valuable an adjunct marker in children with brucellosis to predict OA involvement. However, the use of ESR to predict OA involvement needs further study.

Limitations

There are several limitations to our study. First, this study was conducted at a single center; therefore, it may not be reflective of other regions. However, the data were obtained from patients from a highly endemic region (Turkey) with a large number of children with brucellosis. This study was designed as a retrospective cohort study, and medical records with information such as complaints and clinical findings were collected retrospectively. Therefore, we obtained only limited data from some participants. Nevertheless, this study enabled us to present the clinical and laboratory findings from a large cohort of pediatric patients, particularly the radiologic findings, in a more detailed and comprehensive manner compared with previous studies.

Second, this study population did not have a healthy control group for multivariate analysis. Although we aimed to determine predictive factors, prospective studies can be used to study underlying pathogenesis and risk factors, aside from the epidemiological factors of OA involvement.

The considerable differences in the exact percentages of different presentations reported in the literature may be because of characteristics of the study populations, different imaging techniques, the radio-diagnostic methods used, and different diagnostic criteria used for identifying cases. Moreover, some regional and age-related differences appear to play a role in the incidence, pattern, and presentation of OA brucellosis in children.

This study demonstrated that half of patients had OA involvement and that peripheral arthritis was the most common form of OA involvement in children. Increasing age was associated with both overall OA involvement as well as the specific type of OA involvement. In conclusion, all physicians must be familiar with brucellosis and should consider OA involvement in all children who present with arthritis and arthralgia. Diagnosis and treatment should be done promptly to prevent further complications. These results can help physicians to make early identification and diagnosis of childhood OA brucellosis to enable the disease to be treated before further complications arise.

REFERENCES

1. Pappas G, Akritidis N, Bosilkovski M, et al. Brucellosis. *N Engl J Med*. 2005;352:2325–2336.
2. Shaalan MA, Memish ZA, Mahmoud SA, et al. Brucellosis in children: clinical observations in 115 cases. *Int J Infect Dis*. 2002;6:182–186.
3. Shehabi A, Shakir K, el-Khateeb M, et al. Diagnosis and treatment of 106 cases of human brucellosis. *J Infect*. 1990;20:5–10.
4. Roushan MR, Amiri MJ. Update on childhood brucellosis. *Recent Pat Antiinfect Drug Discov*. 2013;8:42–46.
5. Andriopoulos P, Tsironi M, Deftereos S, et al. Acute brucellosis: presentation, diagnosis, and treatment of 144 cases. *Int J Infect Dis*. 2007;11:52–57.
6. Bosilkovski M, Krteva L, Caparoska S, et al. Childhood brucellosis: Review of 317 cases. *Asian Pac J Trop Med*. 2015;8:1027–1032.
7. Salari MH, Khalili MB, Hassanpour GR. Selected epidemiological features of human brucellosis in Yazd, Islamic Republic of Iran: 1993-1998. *East Mediterr Health J*. 2003;9:1054–1060.
8. Gottesman G, Vanunu D, Maayan MC, et al. Childhood brucellosis in Israel. *Pediatr Infect Dis J*. 1996;15:610–615.
9. Bosilkovski M, Kirova-Urosevic V, Cekovska Z, et al. Osteoarticular involvement in childhood brucellosis: experience with 133 cases in an endemic region. *Pediatr Infect Dis J*. 2013;32:815–819.
10. Tanir G, Tufekci SB, Tuygun N. Presentation, complications, and treatment outcome of brucellosis in Turkish children. *Pediatr Int*. 2009;51:114–119.
11. Dean AS, Crump L, Greter H, et al. Clinical manifestations of human brucellosis: a systematic review and meta-analysis. *PLoS NeglTrop Dis*. 2012;6:e1929e1929.
12. Zamani A, Kooraki S, Mohazab RA, et al. Epidemiological and clinical features of Brucella arthritis in 24 children. *Ann Saudi Med*. 2011;31:270–273.
13. Geyik MF, Gür A, Nas K, et al. Musculoskeletal involvement of brucellosis in different age groups: a study of 195 cases. *Swiss Med Wkly*. 2002;132:98–105.
14. Ma L, Ma J, Chen X, et al. A 10-year retrospective comparative analysis of the clinical features of brucellosis in children and adults. *J Infect Dev Ctries*. 2021;15:1147–1154.
15. Zheng R, Xie S, Lu X, et al. A Systematic Review and Meta-Analysis of Epidemiology and Clinical Manifestations of Human Brucellosis in China. *Biomed Res Int*. 2018;2018:15712920–15712910.
16. Buzgan T, Karahocagil MK, Irmak H, et al. Clinical manifestations and complications in 1028 cases of brucellosis: a retrospective evaluation and review of the literature. *Int J Infect Dis*. 2010;14:e469–e478.
17. Roushan MR, Ahmadi SA, Gangi SM, et al. Childhood brucellosis in Babol, Iran. *Trop Doct*. 2005;35:229–231.
18. Wang W, Wang Z, Jia K, et al. Clinical and Laboratory Characteristics of Childhood Brucellosis in High-Risk Area of Western China. *Jpn J Infect Dis*. 2022;75:127–132.
19. Çiftdoğan DY, Aslan S. Osteoarticular involvement of brucellosis in pediatric patients: clinical and laboratory characteristics. *Turk J Pediatr*. 2020;62:199–207.
20. Tsolia M, Drakonaki S, Messaritaki A, et al. Clinical features, complications and treatment outcome of childhood brucellosis in central Greece. *J Infect*. 2002;44:257–262.
21. Mantur BG, Akki AS, Mangalgi SS, et al. Childhood brucellosis--a microbiological, epidemiological and clinical study. *J Trop Pediatr*. 2004;50:153–157.
22. Guler S, Kokoglu OF, Ucmak H, et al. Human brucellosis in Turkey: different clinical presentations. *J Infect Dev Ctries*. 2014;8:581–588.
23. Sanaei Dashti A, Karimi A. Skeletal Involvement of Brucella melitensis in Children: A Systematic Review. *Iran J Med Sci*. 2013;38:286–292.
24. Bosilkovski M, Krteva L, Caparoska S, et al. Osteoarticular involvement in brucellosis: study of 196 cases in the Republic of Macedonia. *Croat Med J*. 2004;45:727–733.
25. Hashemi SH, Keramat F, Ranjbar M, et al. Osteoarticular complications of brucellosis in Hamedan, an endemic area in the west of Iran. *Int J Infect Dis*. 2007;11:496–500.
26. Logan LK, Jacobs NM, McAuley JB, et al. A multicenter retrospective study of childhood brucellosis in Chicago, Illinois from 1986 to 2008. *Int J Infect Dis*. 2011;15:e812–e817.
27. Taşova Y, Saltoğlu N, Sahin G, et al. Osteoarthricular involvement of brucellosis in Turkey. *Clin Rheumatol*. 1999;18:214–219.
28. Hasanjani Roushan MR, Mohrez M, Smailnejad Gangi SM, et al. Epidemiological features and clinical manifestations in 469 adult patients with brucellosis in Babol, Northern Iran. *Epidemiol Infect*. 2004;132:1109–1114.
29. Kazak E, Akalın H, Yılmaz E, et al. Brucellosis: a retrospective evaluation of 164 cases. *Singapore Med J*. 2016;57:624–629.
30. Gotuzzo E, Alarcón GS, Bocanegra TS, et al. Articular involvement in human brucellosis: a retrospective analysis of 304 cases. *Semin Arthritis Rheum*. 1982;12:245–255.
31. Ebrahimpour S, Bayani M, Moulana Z, et al. Skeletal complications of brucellosis: A study of 464 cases in Babol, Iran. *Caspian J Intern Med*. 2017;8:44–48.
32. Turan H, Serefhanoglu K, Karadeli E, et al. Osteoarticular involvement among 202 brucellosis cases identified in Central Anatolia region of Turkey. *Intern Med*. 2011;50:421–428.
33. Bozgeyik Z, Aglamis S, Bozdag PG, et al. Magnetic resonance imaging findings of musculoskeletal brucellosis. *Clin Imaging*. 2014;38:719–723.
34. Pourbagher A, Pourbagher MA, Savas L, et al. Epidemiologic, clinical, and imaging findings in brucellosis patients with osteoarticular involvement. *AJR Am J Roentgenol*. 2006;187:873–880.
35. Kokoglu OF, Hosoglu S, Geyik MF, et al. Clinical and laboratory features of brucellosis in two university hospitals in Southeast Turkey. *Trop Doct*. 2006;36:49–51.
36. Gómez-Reino FJ, Mateo I, Fuertes A, et al. Brucellar arthritis in children and its successful treatment with trimethoprim-sulphamethoxazole (co-trimoxazole). *Ann Rheum Dis*. 1986;45:256–258.
37. al-Eissa YA, Kambal AM, Alrabeeah AA, et al. Osteoarticular brucellosis in children. *Ann Rheum Dis*. 1990;49:896–900.
38. Gür A, Geyik MF, Dikici B, et al. Complications of brucellosis in different age groups: a study of 283 cases in southeastern Anatolia of Turkey. *Yonsei Med J*. 2003;44:33–44.
39. Solera J, Lozano E, Martínez-Alfaro E, et al. Brucellar spondylitis: review of 35 cases and literature survey. *Clin Infect Dis*. 1999;29:1440–1449.
40. Arkun R, Mete BD. Musculoskeletal brucellosis. *Semin Musculoskelet Radiol*. 2011;15:470–479.
41. Bilgeturk A, Gul HC, Karakas A, et al. Can imaging modalities be used as follow-up criteria after brucellar sacroiliitis treatment? *J Infect Dev Ctries*. 2017;11:123–128.
42. Colmenero JD, Ruiz-Mesa JD, Plata A, et al. Clinical findings, therapeutic approach, and outcome of brucellar vertebral osteomyelitis. *Clin Infect Dis*. 2008;46:426–433.
43. Smailnejad Gangi SM, Hasanjani Roushan MR, Janmohammadi N, et al. Outcomes of treatment in 50 cases with spinal brucellosis in Babol, Northern Iran. *J Infect Dev Ctries*. 2012;6:654–659.
44. Raptopoulou A, Karantanas AH, Poumboulidis K, et al. Brucellar spondylodiscitis: noncontiguous multifocal involvement of the cervical, thoracic, and lumbar spine. *Clin Imaging*. 2006;30:214–217.
45. Esmaeilnejad-Ganji SM, Esmaeilnejad-Ganji SMR. Osteoarticular manifestations of human brucellosis: A review. *World J Orthop*. 2019;10:54–62.
46. Li T, Li W, Du Y, et al. Discrimination of pyogenic spondylitis from brucellar spondylitis on MRI. *Medicine (Baltim)*. 2018;97:e11195.
47. Bosilkovski M, Zezoski M, Siskova D, et al. Clinical characteristics of human brucellosis in patients with various monoarticular involvements. *Clin Rheumatol*. 2016;35:2579–2584.
48. Mehanic S, Baljic R, Mulabdic V, et al. Osteoarticular manifestations of brucellosis. *Med Arch*. 2012;66:24–26.
49. Balın SO, Tartar AS, Akbulut A. The predictive role of haematological parameters in the diagnosis of osteoarticular brucellosis. *Afr Health Sci*. 2018;18:988–994.