Clinical and laboratory features, complications and treatment outcome of brucellosis in childhood and review of the literature

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Brucellosis, whether in an endemic region or not, remains a diagnostic puzzle due to occasional misleading unusual presentations and non-specific symptoms. The aim of this study was to evaluate the clinical and laboratory findings, complications and treatment outcome of brucellosis in children in southeastern Anatolia, Turkey. This study focuses on the frequency of clinical and laboratory findings and complications in cases with brucellosis. Of 22 patients, 8 (36.3%) were female and 14 (63.7%) were male. Fever, malaise, lack of appetite, arthralgia, and night sweating were the main presenting symptoms overall. Hematologic complications (n=13, 59.1%) were most common, followed by skeletal (n=7, 31.8%) and cutaneous system (n=1, 4.5%). Brucellosis may affect any organ system and imitate a variety of clinical entities. Diagnosis of brucellosis should be considered whenever there is a febrile illness associated with rheumatological complaints. Consequently, early recognition of the infection, prolonged antibiotic treatment and careful long-term follow-up should improve the patient outcome.

Key words: brucellosis, children, clinical finding, epidemiology, laboratory finding.

Brucella species are small, non-motile, non-spore-forming, encapsulated Gram-negative coccobacilli. There are seven species, of which only four can cause human brucellosis: *Brucella abortus, Brucella melitensis, Brucella suis*, and *Brucella canis*[1,2]. Brucellosis is a systemic infectious disease and remains an important public health problem throughout the world, but especially in the Mediterranean region, including Turkey[3,4]. Disease incidence and prevalence rates vary widely among nations. Due to variable reporting, true estimates in endemic areas are unknown. According to reports from the Turkish Ministry of Health, 37 cases were reported in 1970, with numbers rising to 18,408 cases in 2004 (incidence rate 25.67/100,000), and it is frequent especially in the rural areas of the middle and southeastern regions, with *B. melitensis* being the most prevalent strain[3,5]. It is thought that this increase is a result of improvements in diagnosis and increased reporting, rather than a real increase in the prevalence of the disease.

The disease is transmitted to man mainly after consumption of unpasteurized milk and milk products and less often after direct contact with infected animals[6]. Following infection, the bacteria initially localize in the regional lymph nodes, and then disseminate hematogenously to the organs of the reticuloendothelial system to multiply within phagocytic cells. The release of bacterial endotoxin from phagocytic cells produces the constitutional symptoms and signs of the disease[7].

The manifestations of brucellosis are not pathognomonic; the clinical diagnosis should always be confirmed with bacteriological or serological tests[4]. However, high fever, myalgia and arthralgia of the large joints are the main symptoms. Brucellosis usually causes abortion

and sterility in animals, while it may lead to a variety of clinical presentations, and even multiple organ involvement, in humans[5]. Because brucellosis is one of the great imitators in the world of infectious diseases, it can mimic various multisystem diseases, showing wide clinical polymorphism, which frequently leads to misdiagnosis and treatment delays, further increasing the complication rates[5,8,9].

Epidemiological studies on brucellosis have suggested that it occurs in all seasons, most commonly in spring and summer, and adults more commonly become seropositive than younger people[2,10,11]. Although it is believed that children are uncommonly involved, a number of reports from endemic areas showed a higher percentage of children involved (20-30% of affected patients)[12]. The majority of illnesses in infected children are also variable, with mild-to-moderate severity[4]. The aim of this study was to evaluate the clinical and laboratory findings, complications and treatment outcome of brucellosis in children in an endemic area, southeastern Anatolia, Turkey, and to compare our findings with reports of other series of childhood brucellosis.

Material and Methods

This study was retrospectively carried out at Midyat State Hospital, Departments of Pediatrics and Infectious Diseases, between April 2007 and August 2008. For its size, Midyat, a small and mostly rural county of approximately 75,000 inhabitants, had an unusually high annual incidence of brucellosis due to poor preventive measures and inadequate public health policies. In this study, patient files of 22 children aged ≤15 years were investigated for demographic characteristics, patients and family history, area of residence, history of the consumption of raw milk or milk products or work in animal breeding, and clinical and laboratory findings, as well as clinical outcomes and complications.

Brucellosis was diagnosed according to the case definition and treatment guidelines of the Turkish Ministry of Health[13]: isolation of microorganisms in blood, other body fluids or tissue samples, or the presence of compatible clinical symptoms such as arthralgia, fever, sweating, chills, headache, myalgia, and malaise, combined with a serum antibody titer ≥1/160 or at least a four-fold increase in this titer by the standard tube agglutination (STA) test in a two- or three-week interval. *B. abortus* S99 antigens (Pendik Veterinary Control and Research Institution, İstanbul, Turkey) were used for the STA. In addition, tests for complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and blood chemistry profile were performed in all patients.

'Focal form or complication' was defined as the presence of symptoms or physical signs of infection at a particular anatomic site in a patient with active brucellosis. Osteoarticular involvement was diagnosed in instances of tenderness, restriction of movement and swelling in any peripheral joint or by unrelieved pain at rest together with radiological alterations. However, swelling was not essential for the diagnosis of hip, spine or sacroiliac arthritis. Diagnoses of spondylitis and sacroiliitis were confirmed by computerized tomography (CT) or magnetic resonance imaging (MRI). 'Hematologic involvement' was defined as hematologic abnormalities in laboratory and clinical findings (epistaxis, bleeding, petechiae, purpura, disseminated intravascular coagulation, and thrombophlebitis), excluding asymptomatic or poorly symptomatic cytopenias or coagulation disturbances. Anemia, thrombocytopenia and leukopenia were defined as hemoglobin level of <10 g/dl, platelet count of <142,000/mm^3 and leukocyte count of <4,600/mm^3, respectively.

When a child with brucellosis was identified, all other siblings in the family were also examined, and STA test was done. Patients were generally treated as outpatients. Outpatients were called for follow-up visits at two-week intervals. At the first follow-up visit, complete blood count, CRP, ESR, and liver enzymes were examined and STA was performed. These tests were repeated at each further follow-up visit until full recovery. They were admitted for inpatient care only if they were aged <5 years, had rectal temperature of >39°C, had arthritis that prevented weight-bearing, failed to improve on oral medication, or had non-compliance to oral medication at home.

For the treatment of brucellosis, the following antibiotics were used: streptomycin 20 mg/

kg/d, once daily, for 15 days, gentamicin 5 mg/kg/d, once daily, for 7 days, doxycycline 4 mg/kg/d in two doses, rifampicin 20 mg/kg/d in two divided doses, and trimethoprim-sulfamethoxazole (TMP-SMX) 8-10 mg/kg/d, for 6 weeks. Different regimens were used during this period but the combination of TMP-SMX and rifampicin was the treatment of choice for most of the patients. Gentamicin or streptomycin was administered to those who had a more severe illness. TMP-SMX was used instead of doxycycline in children <8 years old. When required, the duration of therapy was extended.

Patients were followed up fortnightly until the end of the treatment period, monthly for three months, and thereafter every three months for one year. Relapse was defined as recurrence of symptoms and signs of the disease within one year of the initial diagnosis with persistent high and/or rising antibody titer after treatment, in the absence of re-exposure to infection.

Results

In this study, 22 patients (14 males, 8 females) with brucellosis were analyzed. The male/female ratio was 1.75, and the mean age was 8.9±2.8 years (range: 4-15 years). Two patients (9%) were 0-4 years of age, 13 (59.1%) were 5-10 years of age and 7 (31.9%) were 11-15 years of age. Of the 22 patients, 14 (63.7%) were living in rural areas, 7 (31.8%) in suburban areas and the remaining 1 in an urban area. Land farmers or stock farmers were the parents of all children coming from rural areas and the parents of 3 children from a suburban area. Of the 22 patients, information regarding exposure to risk factors for transmission of brucellosis was recorded in 16 (72.7%). The mode of transmission in those patients was consumption of unpasteurized milk and milk products, especially fresh cheese. The possible source of infection was unknown in 6 (27.3%) cases since the parents could not recall any exposure events. A positive family history for brucellosis was noted in 5 patients (22.8%). Most of the cases (n=19, 86.4%) were admitted to our hospital in the spring and summer months. The seasonal distribution of cases is shown in Fig. 1.

Table I. The Distribution of Age and STA Titers of the Patients According to the Clinical Forms

	Acute (n=18, %)	Subacute (n=3, %)	Chronic (n=1, %)
Age			
0–4	2 (11.1)	-	-
5–10	12 (66.7)	1 (33.3)	-
11–15	4 (22.2)	2 (66.7)	1 (100)
STA titers			
1/160	4 (22.2)	2 (66.7)	1 (100)
1/320	10 (55.6)	1 (33.3)	-
1/640	3 (16.6)	-	-
1/1280	1 (5.6)	-	-

STA: Standard tube agglutination test.

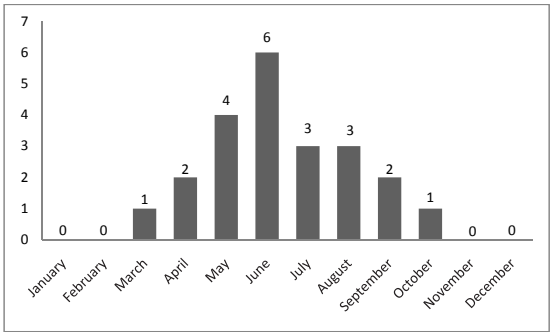

Fig. 1. The seasonal distribution of the cases.

Most patients (81.8%) presented with acute symptoms of no longer than 2 weeks' duration, while 1 patient (4.6%) had a chronic presentation with symptoms before admission of more than 6 weeks; 3 (13.6%) had subacute presentation lasting 2 to 6 weeks (Table I). In all the patients, brucellosis was diagnosed for the first time. Five patients (22.8%) were hospitalized, and included cases of pancytopenia, thrombocytopenia and arthritis (n=3). The remaining 17 patients (77.2%) were followed as outpatients. Mean duration of symptoms prior to admission was 17.4±14.7 days (median: 12 days, range: 7-69 days). Signs and symptoms of brucellosis in this series reflected a combination of systemic illness with certain manifestations. Table II shows the main symptoms and signs noted on presentation. The severity of symptoms varied from mild illness to severe painful localized disease. Fever, malaise, lack of appetite, arthralgia, and night sweating were the main presenting symptoms overall. The commonest abnormalities on physical examinations were fever, hepatomegaly and arthritis.

Table II. Clinical Characteristics in 22 Patients with Brucellosis

Symptoms	n (%)	Findings	n (%)
Fever	20 (90.9)	Fever*	17 (77.2)
Malaise/Weakness	19 (86.4)	Hepatomegaly	7 (31.8)
Lack of appetite	15 (68.1)	Arthritis	5 (22.8)
Arthralgia	12 (54.6)	Splenomegaly	4 (18.2)
Night sweating	11 (50)	Hepatosplenomegaly	3 (13.6)
Myalgia	8 (36.3)	Lymphadenopathy	1 (4.5)
Lumbar pain	5 (22.8)	Rash	1 (4.5)
Chills	4 (18.2)		
Headache	4 (18.2)		
Abdominal pain	4 (18.2)		
Weight loss	3 (13.6)		
Vomiting	2 (9.1)		

*Fever was defined as axillary and rectal temperature of >37.3°C and >38.3°C, respectively.

The most common laboratory findings were high ESR (normal range, <20 mm/h) (90.9%) and high CRP (normal range, 0-8 mg/dl) (86.3%) levels and anemia (40.9%). While 16 patients (72.8%) had normal leukocyte counts (4,600-10,200/mm^3), leukopenia was found in 4 cases (18.2%), leukocytosis in 2 cases (9%), and pancytopenia in 1 case (4.5%). Thrombocytopenia was seen in 13.6% of the whole group and the counts for 2 patients were 48,000/mm^3 and 54,000/mm^3. Raised liver function tests were seen in 54.6% of the patients. The STA test was positive in all patients, with titers ranging from 1/160 to 1/1280. The STA titers of the patients, initially and at the end of the treatment, and according to the clinic forms are listed in Tables III and Table I, respectively. After a 6-week course, STA titers of all patients decreased to <1/160, except in 1 who had spondylitis. Blood cultures were performed in 9 patients (40.3%) and were positive in 2 (9%) of them. However, bone marrow culture was positive in 1 patient who had pancytopenia. The rest of the initial laboratory results are shown in Table IV.

Hematologic complications (59.1%) were most common, followed by skeletal and cutaneous systems (Table V). None of the children had signs or symptoms of central nervous, cardiovascular, respiratory, gastrointestinal, or genitourinary system complications. Osteoarticular complications were the most frequent focal forms, present in 7 cases, representing 31.8% of all patients. Of the 22 patients, 12 had arthralgia in joints other than the joints affected by arthritis. The arthralgia manifested as intermittent or migratory pain of large or small joints, or both, with or without limitation of movements. The most frequently involved joint with arthralgia was the knee joint (n=6), followed by the hip (n=3), ankle (n=1), sternoclavicular (n=1), and sacroiliac (n=1). However, we defined arthritis as painful limitation of the range of movement or the presence of signs of inflammation around the joint. Arthritis was found in only 5 patients (22.7%), and the most commonly affected joint was the knee joint (n=4), with predominantly unilateral involvement. Plain radiographs, obtained in 12 patients, generally showed normal findings (n=9) or merely confirmed periarticular soft tissue swelling (n=2) or intraarticular effusion (n=1). Spondylitis was diagnosed by using MRI, and sacroiliitis was established using CT. One of the patients had a maculopapular rash related to the disease.

Various initial regimens were administered to the 22 patients with brucellosis (Table VI). The response of joint symptoms to the treatment was immediate, and the majority of the patients had significant improvement. The duration of treatment was 6 weeks in 21 patients (95.5%), and 90 days in 1 patient with spondylitis. A combination of rifampicin and TMP-SMX with or without gentamicin was used in most of the patients. All of the patients had a complete therapy and follow-up; 21 had complete recovery and 1 (4.5%) relapsed after stopping therapy. This patient recovered after a new regimen was used. No mortality was registered in our patients.

Table III. STA Titers of the Patients

STA titers	Initial (n, %)	End of treatment (n, %)
0	-	1 (4.5)
1/20	-	5 (22.8)
1/40	-	9 (40.9)
1/80	-	7 (31.8)
1/160	7 (31.8)	-
1/320	12 (54.6)	-
1/640	2 (9.1)	-
1/1280	1 (4.5)	-

STA: Standard tube agglutination test.

Discussion

Brucellosis remains an important public health problem in our region that can cause serious complications and significant morbidity. It can affect people of any age, including children. Childhood brucellosis has long been considered an uncommon disease, as children make up 10% to 25% of all cases[1,4]. This relatively low incidence has been attributed to the following: other diseases have similar manifestations, the disease is mild in children compared to adults, and brucellosis is infrequently considered in childhood[1]. Brucellosis in children, in contrast to adults, may be self-limited, with spontaneous recovery likely to occur[14]. Among 112 cases that were reviewed during the study period, 22 (19.6%) were children. This ratio is similar to that of Al Shaalan et al.'s[1] study (21%). In our study patients, there was an obvious preponderance of males, as can be seen in Table VII, and this is in accordance with other studies performed in our country as well as in other countries[4,6,7,11,12,14-17]. In agreement with other studies[4,7], all age groups were susceptible to the infection, but children older than five years were more often affected. A probable explanation is that the older boys were more involved in animal care. Consumption of raw milk and milk products and to a lesser extent contact with infected animals or their waste materials are the main routes of infection in children[3,4,12]. In this study, consumption of unpasteurized dairy products, especially fresh white cheese, was the most common mode of transmission. Approximately all of the patients were children or grandchildren of farmers. It was determined from patient histories that there were past and present brucellosis cases among family members of some of the patients. None of them had symptomatic infection. It was reported that brucellosis among other family members is common and must be taken into consideration[4,6,18].

Brucellosis is a multisystem disease with a broad spectrum of non-specific symptoms that generally occur within two weeks (but sometimes up to three months) after inoculation[19]. Brucellosis may appear in four different forms, namely acute, subacute, chronic, and relapse[2,5]. In this study, the acute presentation constituted most of the cases (81.8%), whereas subacute and chronic cases constituted 13.6% and 4.5% of the cases, respectively; this is in accordance with Al Shaalan et al.'s[12] study. However, Tanir et al.[4] reported a higher rate (24.4%) of the chronic form of brucellosis in our country, which can be explained by treatment failure or hyperendemicity in our country.

The clinical manifestations of brucellosis are protean, and the severity of the disease depends on the Brucella species. *B. melitensis* is more pathogenic than the other species and

Table IV. The Laboratory Findings of the Cases

Variables	n (%)
WBCc/mm^3	
<4600	4 (18.2)
4600-10200	16 (72.7)
>10200	2 (9.1)
Hemoglobin <10 g/dl	9 (40.9)
Platelet <142000	3 (13.6)
ALT >35 IU/L	8 (36.4)
AST >40 IU/L	12 (54.6)
GGT >50 IU/L	2 (9)
ALP >128 IU/L	7 (31.8)
Total bilirubin >1.2 mg/dl	2 (9)
ESR >20 mm/h	20 (90.9)
CRP >8 mg/dl	19 (86.3)
Positive blood culture	2 (9.1)
Positive bone marrow culture	1 (4.5)

WBCc: White blood cell count. ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. GGT: γ-glutamyl transpeptidase. ALP: Alkaline phosphatase. ESR: Erythrocyte sedimentation rate. CRP: C-reactive protein.

Table V. Complications in 22 Patients with Brucellosis

Complications	n (%)
Hematologic system	13 (59.1)
Anemia	9 (40.9)
Thrombocytopenia	3 (13.6)
Pancytopenia	1 (4.5)
Skeletal system	7 (31.8)
Peripheral monoarthritis	5 (22.8)
Sacroiliitis	1 (4.5)
Spondylitis	1 (4.5)
Cutaneous system	
Rash	1 (4.5)
More than one complication	8 (36.4)

produces more intense symptoms[1]. It was also the most commonly isolated organism in our series; most of the patients presented within two weeks of onset of their symptoms. This observation is in agreement with previous reports[12,17]. Most of the present patients had uncomplicated brucellosis with the main clinical symptoms being fever, malaise/weakness, lack of appetite, arthralgia, and night sweating. The other presenting symptoms were myalgia, lumbar pain, chills, headache, abdominal pain, weight loss, and vomiting. Fever, hepatomegaly, arthritis, splenomegaly, lymphadenopathy, and rash were presenting signs. As can be seen in Table VIII, the clinical characteristics of childhood brucellosis in our series are similar to those reported by previous studies [5-7,12,15,17,20,21].

As the symptoms of brucellosis are not specific, confirmation can be reached with serological tests, with significantly raised or rising titer, in the presence or absence of blood culture. Isolation of Brucella spp. from the blood, bone marrow or other tissue fluids is the hallmark of diagnosis[9,22]. As can be seen in Table IX, the rate of isolation from blood is generally low, varying from 7% to 74.3% depending on the methodology used[4,6,11,15-17,20]. Previous antibiotic use significantly decreases the likelihood of bacterial isolation in blood cultures[5]; for this reason, we could not isolate Brucella spp. in the four patients in whom blood culture was performed. Serologic tests are the main tools of diagnosis of brucellosis. SAT for Brucella with titers ≥1/160 is suggestive of active infection. The sensitivity of the serological tests ranges from 65% to 95%, but their specificity is low because of the high prevalence of antibodies in the healthy population[4]. However, antibody detection is not always sufficient to indicate the existence of active infection, especially in endemic areas[23]. Therefore, diagnosis of brucellosis should be performed according to international or national case definitions. In this study, our national case definition in the diagnosis of brucellosis was applied, and ESR >20 mm/h, increased CRP, increased liver enzymes, and anemia were the most prominent laboratory abnormalities.

The clinical manifestation of brucellosis varies greatly, ranging from asymptomatic infection to serious debilitating disease. Organ involvement can be assigned as focal involvement or as a complication. For the most part, brucellosis is a systemic infection that can involve any organ of the body[24]. Cutaneous, hematological and respiratory complications in children; locomotor and cardiac complications in adults; and genitourinary, neurological and gastrointestinal complications in middle-aged individuals were more prominent[4,7]. In this study, no patient presented with neurological, respiratory, cardiac, or genitourinary complications. Complications of brucellosis represent a major medical problem in countries where brucellosis is still endemic, as in our region of southeastern Anatolia in Turkey.

Hematological alterations in brucellosis are common, but they rarely constitute a true complication and resolve promptly with treatment[25]. The hematological manifestations of brucellosis include anemia, leukopenia, neutropenia, thrombocytopenia, and pancytopenia[26]. Anemia in patients with brucellosis results from alteration in iron metabolism secondary to infection,

Table VI. Antibiotic Combinations Administered to Patients with Brucellosis

	n	%
TMP-SMX + rifampicin	12	54.6
Doxycycline + rifampicin	4	18.2
TMP-SMX + rifampicin + gentamicin	3	13.6
Doxycycline + rifampicin + gentamicin	2	9.1
Doxycycline + streptomycin	1	4.5

TMP-SMX: Trimethoprim-sulfamethoxazole.

Table VII. Comparison of Gender, Age and Clinical Types of Brucellosis in Various Studies

	Country	No. of cases	Female (%)	Male (%)	Mean age	Acute (%)	Subacute (%)	Chronic (%)
Palanduz et al. (15)	Turkey	43	46.5	53.5	6.9±2.5 years	100	-	-
Tanir et al. (4)	Turkey	90	30	70	9.02±3.59 years	36.7	38.9	24.4
Al Shaalan et al. (12)	Saudi Arabia	115	36	64	5.8 years 115±42.7 months	75.7	15.6	8.7
Tsolia et al. (6)	Greece	39	41	59	-	-	-	-
El-Amin et al. (16)	Oman	375	46	54	5.6±3.3 years	-	-	-
Giannakopoulos et al. (8)	Greece	52	40.4	59.6	11 years*	-	-	-
Sharda et al. (17)	Kuwait	200	44	56	6.8 years	-	-	-
Issa et al. (11)	Jordan	68	41.2	58.8	-	-	-	-
Feiz et al. (14)	Iran	95	47.4	52.6	9.7 years*	100	-	-
Present study	Turkey	22	36.3	63.7	8.9±2.8 years	81.9	13.6	4.5

(*Median age)

hypersplenism, bleeding, and bone marrow suppression or autoimmune hemolysis[27]. The incidence of anemia has been reported as 43.6% to 74% in brucellosis in adult series[2,26,28]. This ratio was 38.6%, 44% and 58.1% in the studies of Tsolia et al.[6], Al-Eissa et al.[27] and Palanduz et al.[15], respectively. In our patient group, incidence of anemia was 40.9%, which was higher than in the other studies[4,11,12]. However, this ratio was 15.5% in children without any disease in our region[29]. Earlier literature has emphasized the characteristic picture of a normal or reduced leukocyte count with relative or absolute lymphocytosis in patients with brucellosis[26,27]. Leukopenia has been found to occur in 7.7% to 54% of the reported cases (Table IX). In this study, 72.8% of the patients had a normal leukocyte count and 18.2% had leukopenia. Leukopenia was detected in 7.7%, 30% and 54% in the studies of Tsolia et al.[6], Sharda et al.[17] and Issa et al.[11], respectively. The cause of leukopenia seems to be multifactorial. Thrombocytopenia is less common, having been reported in only 1.7% to 15% of cases (Table IX), and it is rarely severe enough to cause bleeding[30]. Although the mechanism of the thrombocytopenia in brucellosis is not yet entirely known, it may be hypersplenism, bone marrow suppression due to septicemia, hemophagocytosis, granulomas, or peripheral immune destruction of thrombocytes[26]. While thrombocytopenia was detected in 13.6% of patients in this study, it was detected at a higher rate (28%) in Benjamin et al.'s[31] study. Pancytopenia has been described as between 2% to 14% in patients with brucellosis in the published series[17,27]. In this study, the incidence of pancytopenia was 4.5%, similar to the results reported by Issa et al.[11] and Palanduz et al.[15]. A number of mechanisms have been implicated in the pathogenesis of pancytopenia in brucellosis. They are similar to the mechanism of thrombocytopenia[16]. However, Al-Eissa et al.[27] concluded that brucellosis may be considered in epidemiologically suspected patients whose blood picture indicates hemolytic anemia, leukopenia, thrombocytopenia, or pancytopenia.

As can be seen in Table X[4,6,11,12,15-17], osteoarticular involvement occurs in 7.7% to 79.1% of cases. In this study, osteoarticular involvement was observed in 31.8% of the

Table VIII. Comparison of Symptoms and Signs in Various Studies

	Sharda et al. (17)	Al-Eissa et al. (20)	İnce et al. (21)	Al Shaalan et al. (12)	Tsolia et al. (6)	Giannakopoulos et al. (8)	Palanduz et al. (15)	Buzgan et al. (5)	+
Publication year	1986	1990	1999	2002	2002	2006	2007	2010	
Symptoms (%)									
Fever	70	93	97	87.8	-	81	95.3	71.8	90.9
Malaise/Weakness	67	-	76	18.2	17.9	19	37.2	55.1	86.4
Lack of appetite	-	45	-	-		14	-	37.2	68.1
Arthralgia	74	90	48	73	69.2	83	18.6	85.9	54.5
Night sweating	22	15	41	8.6	20.5	15	-	50	50
Myalgia	-	60	-	-	-	14	-	17.9	36.3
Lumbar pain	-	20	3	-	-	-	-	-	22.7
Chills	-	-	-	18.2	-	5.7	-	-	18.1
Headache	22	-	34	7	5.1	2	13.9	-	18.1
Abdominal pain	-	-	3	-	-	-	27.9	25.6	18.1
Weight loss	-	50	-	-	10.2	-	16.2	35.9	13.6
Vomiting	-	-	-	-	-	8	-	-	9
Signs (%)									
Fever	-	-	-	91.3	94.8	-	60.4	28.2	77.2
Hepatomegaly	5.1	20.1	41	13	28.2	69	34.8	17.9	31.8
Arthritis	30.1	9.4	13.8	71.3	43.6	12.1	11.6	21.8	22.7
Splenomegaly	2	25	58	12.1	38.5	48	44.1	14.1	18.1
Lymphadenopathy	-	20	13	-	7.7	29	6.9	-	4.5
Rash	-	-	20	1.7	-	-	-	-	4.5

Table IX. Comparison of Laboratory Findings in Various Studies

	Palanduz et al. (15)	Tanir et al.(4)	Al Shaalan et al.(12)	Tsolia et al. (6)	Al-Eissa et al. (20)	Issa et al. (11)	Sharda et al. (17)	El Amin et al. (16)	Present study
Laboratory findings (%)									
Anemia	58.1	26.7	25	38.6	40	24	-	-	40.9
Leukopenia	9.3	10	9.5	7.7	35	54	30	14	18.1
Leukocytosis	7	1.1	22.6	2.6	-	-	14	-	9
Thrombocytopenia	9.3	3.3	1.7	7.7	-	10	2	15	13.6
Pancytopenia	2.3	-	-	-	-	6	2	-	4.5
ESR >20 mm/h	90.7	86.7	73.8	35.5*	71	-	75	21	90.9
Increased liver enzymes	18.6	20	18.3	-	40	-	83.5	-	54.5
Increased CRP	97.7	81.1	-	20*	33	-	-	-	86.3
STA positive (≥1/160)	97.7	91.1	97.3	84.6	100	91.2	100	-	100
Positive culture									
Blood	7	17.8	34.8	74.3	71	23.5	42	38	9
Others**	2.3	-	3.4	3.4	15	-		-	4.5

*Median value. **Cerebrospinal, bone marrow, peritoneal and synovial fluid
ESR: Erythrocyte sedimentation rate. CRP: C-reactive protein. STA: Standard tube agglutination test.

cases, similar to that found by Sharda et al.[17]. The enormous range between reports in the literature may be due to characteristics of the study populations, the radiodiagnostic methods used or the different diagnostic criteria employed. Peripheral arthritis, especially presenting as monoarthritis, is the predominant involvement in some childhood brucellosis series, and large joints such as the hips and knees are the most frequently affected[6,20,32]. Unlike in adults, the sacroiliac joint and axial skeleton were rarely affected[8,32]. Monoarthritis may create confusion with pyogenic arthritis in children; therefore, in a community in which brucella is common, awareness about this entity should prompt investigation of this disease, and physicians should have a high index of suspicion for brucella arthritis[12]. In this study, peripheral arthritis was the most frequent type of osteoarticular involvement, although the rate (22.7%) was higher than that reported by Tanir et al.[4] and Palanduz et al.[15]. The incidence of spondylitis in adults reported in the literature varies significantly, ranging from 6% to greater than 50%[25,33]. In the present study, the rate of spondylitis was 4.5% of 22 patients. On the other hand, osteomyelitis and subluxation of the femoral head have been reported rarely as a complication in children with brucellosis[6,12], and none of our patients had these clinic forms.

Less than 5% of brucellosis patients exhibit non-specific skin symptoms, such as erythema, papules, petechiae, urticaria, impetigo, eczematous rash, erythema nodosum, subcutaneous abscess, and cutaneous vasculitis[5]. This ratio was 1.7% in Al Shaalan et al.'s[12] study and 4.5% in the present study. It is important to emphasize that cutaneous lesions are not specific to brucellosis and may be seen in a variety of other dermatologic diseases caused by many agents.

Gastrointestinal system symptoms, including anorexia, nausea, vomiting, diarrhea, abdominal pain, and gastrointestinal bleeding can be seen in brucellosis[28]. It has been suggested that the diarrhea and abdominal pain in brucellosis might be due to mesenteric adenitis or inflammation and ulceration of the Peyer's patches[4]. Liver and spleen enlargement with mild non-specific elevation of liver enzyme levels can be detected in approximately 50%

Table X. Systems Involvement and Rates in Childhood Brucellosis in Various Studies

	No. of cases	Osteoarticular	Hematological	Central nervous system	Gastrointestinal system	Cardiovascular	Respiratory	GUS	Skin
Palanduz et al. (15)	43	5 arthritis	4 thrombocytopenia 1 pancytopenia	-	-	-	-	-	-
Tanir et al. (4)	90	6 arthritis 1 discitis	3 thrombocytopenia	1 meningitis 1 meningoencephalitis	-	-	-	-	-
Al Shaalan et al. (12)	115	82 arthritis 9 osteomyelitis	2 thrombocytopenia 1 myelodysplastic syndrome	3 neurobrucellosis	1 hepatitis 2 acute abdomen/ diarrhea	1 myocarditis	1 pneumonia	1 nephritis	2 rash
Tsolia et al. (6)	39	17 arthritis	3 thrombocytopenia 1 thrombocytopenic purpura	1 acute facial nerve palsy	-	-	-	-	-
El Amin et al. (16)	375	188 arthritis	56 thrombocytopenia	1 cerebellar ataxia	1 peritonitis 1 cholecystitis	-	-	-	-
Sharda et al. (17)	200	60 arthritis 2 osteomyelitis	4 thrombocytopenia 4 pancytopenia	-	-	3 myocarditis 2 endocarditis	-	-	-
Issa et al. (11)	68	37 arthritis	7 thrombocytopenia 4 pancytopenia	-	-	-	-	-	-
Present study	22	5 arthritis 1 spondylitis 1 sacroiliitis	3 thrombocytopenia 1 pancytopenia	-	-	-	-	-	1 rash

GUS: Genitourinary system.

of all patients with brucellosis[34]. On the other hand, all cases with elevated liver enzymes should not be evaluated as liver involvement. Hepatic involvement has been reported in the literature in around 2% to 3% of cases [5,25,30]. While hepatitis is common, it is usually subclinical, and jaundice is rare[35]. Lulu et al.[36] reported 40% hepatic involvement in their study, namely 1% clinical hepatitis and 38.5% anicteric hepatitis. In this study, liver enzyme elevation was observed in 54.5% of the cases, and a diagnosis of clinical hepatitis was made in none of them. Brucella is also a rare cause of liver abscess, acute cholecystitis, pancreatitis, and spontaneous peritonitis[9].

In brucellosis, the aim of the treatment regimen is to control the acute illness and to prevent both complications and relapses[25]. Because Brucella spp. are intracellular pathogens, any regimens capable of penetrating into the cells and prolonged treatment with a combination of agents are requisites for achieving eradication of the organisms[37]. TMP-SMX and rifampicin penetrate into cells in sufficient concentrations[37]. Optimal treatment of brucellosis remains based on traditional combinations of doxycycline with either rifampicin or streptomycin[38]. Doxycycline is not recommended for children younger than 8 years of age because of the side effects on teeth[12]. Gentamicin for 5 days plus TMP-SMX for six weeks or TMP-SMX plus rifampicin for six weeks are the commonly used regimens of therapy in childhood brucellosis[4]. Patients were treated with diverse therapeutic regimens, since the study is retrospective. In this study, the standard of six weeks combination therapy was adopted, and the present results show that treatment of childhood brucellosis with TMP-SMX + rifampicin or doxycycline + rifampicin, according to the age of the patients, is an effective treatment with low relapse rates (4.5%). However, we did not encounter any side effects to antibiotics during the treatment period, and the compliance of patients and their parents for completion of the treatment course was good. Therapy of six weeks' duration was found to be successful in the majority of patients. Despite treatment including several antibiotic regimens, relapse is estimated to occur in 5% to 40% of patients with acute brucellosis in the following year, depending on antibiotic use, duration of treatment and drug combination[5]. Relapse rates up to 10% are reported with TMP-SMX plus rifampicin[4]. With six weeks of the same regimen, relapse rates of 3.5% and 9% were reported by Khuri-Bulos et al.[39] and Al-Shaalan et al.[12], respectively. Hendricks et al.[1] reported no relapses in children less than 7 years of age treated by this regimen for six weeks. We conclude that six weeks of therapy with TMP-SMX and rifampicin is sufficient for treatment of children with brucellosis.

In conclusion, brucellosis will continue to be a public health problem in countries where consumption of raw milk and/or its products and stockbreeding are widespread. The disease has a significant morbidity and mortality. Brucellosis in children has a wide range of clinical manifestations. It may affect any organ system and imitate a variety of clinical entities. Diagnosis of brucellosis should be considered whenever there is a febrile illness associated with rheumatological complaints. Treatment with at least two antibiotics, especially TMP-SMX and rifampicin, for six weeks or more appears to be effective. Consequently, early recognition of the infection, prolonged antibiotic treatment and careful long-term follow-up should improve the patient outcome.

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