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Original Article

Clinicoepidemiological findings of childhood brucellosis in a tertiary care center in Central Anatolia: with the emphasis of hematological findings

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ABSTRACT

Background. Human brucellosis is one of the most widespread zoonotic diseases that are presented with predominantly hematological manifestations. We aimed to evaluate the hematological findings of childhood brucellosis and to determine the predictive clinical findings and laboratory tests that might be related to hematologic involvement.

Methods. We retrospectively analyzed the medical records of children with brucellosis between 1 January 2005 and 31 December 2018. We compared predictive clinical and physical examination findings and laboratory tests in patients with and without hematological involvement.

Results. A total of 212 patients (127 boys (59.9%)) with a mean age of 9.4±4.7 years were evaluated in this study. Blood cultures were performed in 161 (75.9%) patients and *Brucella* spp were isolated in 70 (43.4%) of them. Ninety-two (43.4%) patients had hematological involvement at least in one series. Anemia was detected in 66 (31.7%) patients, leukopenia in 22 (10.6%) and thrombocytopenia in 10 (4.8%). Four patients (1.9%) had pancytopenia. Age distrubutions of the patients with and without hematological involvement were similar (p=0.6). In patients presented with fever, hepatomegaly and splenomegaly, hematologic involvement was significantly higher (p<0.05). Hematological involvement was higher in patients who had elevated aspartate aminotransferase and alanine aminotransferase concentrations (p<0.05). Hematological involvement was higher in patients with positive blood culture (p=0.005). Six patients (2.8%) were treated with intravenous immunoglobulin at 1000 mg/kg/day for two days in addition to anti-brucellosis treatment.

Conclusions. Hematological involvement in brucellosis is a common finding regardless of age, especially in febrile, bacteremic patients and in patients who had hepatosplenomegaly and elevated liver enzymes. Anemia is the most common hematological abnormality.

Key words: brucellosis, children, cytopenia, hematological findings.

Human brucellosis is one of the most widespread zoonotic diseases and a public health problem in many countries of the Mediterranean and Middle East where bovine brucellosis has not been controlled. It can affect people at any age including children. Approximately 20-30% of cases are diagnosed during childhood.[1-3] Humans can acquire infections via consumption of infected unpasteurized milk and milk products or direct contact with infected animals, secretions and carcasses. Brucellosis is a multisystemic disease which can be presented with various non-specific clinical signs. The most common clinical manifestations include arthralgia, fever, sweating, weight loss, fatigue, and anorexia.[1] Some of these

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patients can be presented with hematological manifestations such as mild anemia, leukopenia and less frequently pancytopenia and thrombocytopenia. Brucellosis may mimic many hematologic diseases, especially in patients presenting predominantly with hematological findings.[2,4]

In this study, we aimed to evaluate the hematological findings of childhood brucellosis and to determine the predicting clinical and physical examination findings and laboratory tests that might be related to hematologic involvement in the setting of a tertiary care pediatric hospital.

Material and Methods

We retrospectively analyzed the medical records of children with brucellosis who were admitted to a referral tertiary care pediatric hospital between 1 January 2005 and 31 December 2018. This study was conducted in compliance with the ethical principles according to the Declaration of Helsinki, and it was approved by the Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital Institutional Review Board (Number: 2019/8). Data regarding age, sex, family history of brucellosis, occupation, fresh milk product consumption history, clinical complaints, physical examination findings and laboratory results were recorded. Organomegaly was assessed with physical examination. Laboratory tests including complete blood count [total leukocyte, absolute neutrophil, absolute lymphocyte, platelet count and mean platelet volume (MPV)], C-reactive protein (CRP), erythrocyte sedimentaton rate (ESR), serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations, blood culture, brucella agglutination tests, bone marrow aspiration smear results if had been applicated and treatment data were evaluated. Brucellosis was diagnosed on the basis of epidemiological and clinical findings, together with positive serum agglutination test (SAT) ≥1/160 titers and/or Brucella immune capture test with Coombs ≥1/160 titers and/or isolation of *Brucella* spp. from blood culture. Agglutination titer range was set at 1/20–1/5120 for each serum sample to avoid false negative results in consequence of prozone effect. Hematological findings were defined as follows: Thrombocytopenia, a platelet count <150.000/μL, leukopenia and anemia, a level lower than age-determined references. Pancytopenia was defined as abnormally low counts of white cells, platelets and low level of hemoglobin in the same patient.[5]

Data were entered to a database and statistical analyses were performed using IBM SPSS Statistics (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). The variables were investigated using visual and analytical methods (Kolmogrov-Simirnov/Shapira-Wilk test) to determine whether or not they are normally distributed. Descriptive analyses were presented using means ± standard deviations for normally distributed variables and as medians (minimum-maximum) for the non-normally distributed and ordinal variables. Frequencies were given to summarize the categorical variables. The chi-square test or Fisher's exact test was used to compare patients with or without hematological involvement. The correlation coefficients and their significance were calculated using the Pearson test between SAT titer and mean platelet volume. A p-value less than 0.05 was considered a statistically significant result.

Results

A total of 212 patients [127 boys (59.9%)] diagnosed with brucellosis were evaluated in this study. Age distribution was from one day old neonate to 17.9 years. Median age of the patients was 9.4 years (SD 4.7 years) and 10.09 years (IQR: 5.35 years-13.3 years). Four (1.8%) patients were younger than one year of age (one patient was a preterm neonate, one patient an exclusively breast-fed young infant, two patients complementarily fed babies including

unpasteurized cheese), 45 patients were between 1-5 years, 87 patients were between 5-12 years, and 76 patients were ≥12 years. None of the patients had a known hematologic disease. One hundred and twenty eight (60.4%) patients were hospitalized for a mean duration of 11±6.7 days. A total of 183 (86.3%) patients had a history of consuming unpasteurized milk and dairy products. At least one parent of 121 patients (57.1%) were working in animal breeding and had intimate contact with sheep and/or cows. Eighty-four (39.6%) patients had positive family history for brucellosis. The symptoms and physical examination findings were shown in Table I. Median duration of fever was 15 days (range 1-365 days). The most commonly involved joint was knee in 21 (65.6%) patients, followed by ankle in seven (21.9%) patients and hip in four (12.5%) patients. Nine (75.0%) patients had cervical, two (16.7%) had inguinal, and one (8.3%) had mesenteric lymphadenopathy. Blood cultures were performed in 161 (75.9%) patients and *Brucella* spp were isolated in 70 (43.4%) of them. Serum agglutination test titers at presentation were ≥1/160 in 201 patients (94.8%). Ten (4.7%) patients with SAT titers of <1/160 were diagnosed with positive blood culture.

Table I. The clinical symptoms and physical examination findings of patients with brucellosis.

	Patient number	%
Clinical symptoms		
Arthralgia	154	72.6
Fever	119	56.1
Weight loss	46	21.7
Night sweats	30	14.2
Arthritis	36	17
Headache	17	8
Abdominal pain	17	8
Physical examination findings		
Hepatomegaly	38	17.9
Fever	35	17.5
Arthritis	32	15.1
Splenomegaly	28	13.2
Lymphadenopathy	12	5.7

Ninety-two (43.4%) patients had hematological involvement at least in one lineage. The initial complete blood count findings of patients were summarized in Table II. On admission, anemia was detected in 66 (31.7%) patients, leukopenia was detected in 22 (10.6%) patients [14 (6.7%) neutropenia, 14 (6.7%) lymphopenia], and thrombocytopenia was detected in 10 (4.8%) patients. Four patients (1.9%) had pancytopenia. The epidemiological and laboratory findings of patients presenting with pancytopenia were shown in Table III. Aspartate aminotransferase and ALT levels were ≥40 IU/L in 69 (32.5%) and in 55 (25.9%) patients, respectively.

The mean age of patients with and without hematological involvement were 9.6±4.5 years and 9.3±4.8 years, respectively (p=0.6). Hematologic involvement was higher in patients with fever (p<0.001). There was no association between duration of fever and hematologic involvement (p=0.68). In patients who had hepatomegaly and splenomegaly, hematologic involvement was statistically higher (p=0.001 and p=0.005, respectively). Hematological involvement was also higher in those who had elevated AST and ALT levels (p<0.05). The presence of hepatomegaly and splenomegaly, results of blood cultures and transaminase concentrations of patients with and without hematologic involvement were shown in Table IV. Mean platelet volume was 8.1 ± 0.95 fL, and there was no correlation between SAT titer and mean platelet volume (r = -0.02, p = 0.7). It was found that SAT titers were not correlated with the presence of hematologic findings (p=0.55). Hematological involvement was higher in patients with positive blood culture (p=0.005). Bone marrow aspiration was performed in 14 (15.2%) patients with hematological impairement. In one patient with pancytopenia, the bone marrow aspiration revealed multiple hemophagocytic histiocytes, in four patients (one patient with leukopenia and thrombocytopenia, three patients with anemia and leukopenia) revealed a few number of hemophagocytic histiocytes. Two patients with pancytopenia had normal bone marrow

Table II. The initial complete blood count findings of patients.

Parameter	All patients (mean ± SD)	Hematologic involvement present (mean ± SD)	Hematologic involvement absent (mean ± SD)
Hemoglobin (g/dL)	12 ± 1.4	10.5 ± 1.1	12.7± 0.9
Total leukocyte (/mm^3)	7450 ± 4735	3700 ± 916	7907 ± 4810
Absolut neutrophil (/ mm^3)	3267± 1965	1067± 330	3471± 1929
Absolute lymphocyte (/ mm^3)	3411± 2686	1321± 315	3605± 2727
Platelet (/mm^3)	284.509± 97.585	93.785± 37.529	297.994± 85.667

Table III. Epidemiological and laboratory findings of patients with pancytopenia.

Patient number	Age (month)	Gender	Hb g/dL	WBC /mm^3	Nuetrophil /mm^3	Lymphocyte /mm^3	Platelet /mm^3	ESR mm/h	CRP mg/L	SAT	Blood culture
1	145	F	11.4	2600	900	1410	140.000	28	101	1/320	*Brucella* spp.
2	91	M	8.5	1800	830	710	69.000	-	39	1/640	*Brucella* spp.
3	173	F	10.8	2900	1400	1000	70.000	120	77	1/5120	No growth
4	178	F	9.5	1800	770	930	62.000	30	11	1/640	*Brucella* spp.

Hb: hemoglobin, WBC: white blood cell, ESR: erythcyte sedimentaton rate, CRP: C-reactive protein, SAT: serum agglutination test

Table IV. Hepatomegaly, splenomegaly, transaminase and blood culture results in patients with and without hematologic involvement.

	Hematologic involvement present n / %	Hematologic involvement absent n / %	p value
Hepatomegaly			
Positive	26 (68.4%)	12 (31.6%)	p=0.001
Negative	66 (37.9%)	108 (62.1%)	
Splenomegaly			
Positive	19 (67.9%)	9 (32.1%)	p=0.005
Negative	72 (39.3%)	111 (60.7%)	
ALT			
Normal	58 (37.9%)	95 (62.1%)	p=0.005
>40 IU/L	33 (60%)	22 (40%)	
AST			
Normal	49 (35.3%)	90 (64.7%)	p<0.001
>40 IU/L	42 (60.9%)	27(39.1%)	
Blood culture			
Brucella spp.	41 (58.6%)	29 (41.4%)	p=0.005
No growth	33 (36.3%)	58(63.7%)	

AST: aspartate aminotransferase, ALT: alanine aminotransferase

aspiration smears. All of the patients were treated with combination regimens (doxycycline plus rifampicin for patients older than eight years and cotrimoxazole plus rifampicin for those younger than eight years). Six patients (2.8%) were treated with intravenous immunoglobulin (IVIg) (1 g/kg/day, for two days) in addition to anti-brucellosis treatment.

Discussion

In the present study, anemia was found as the most common hematological finding of brucellosis followed by leukopenia, thrombocytopenia, and pancytopenia. We found that the presence of hematological involvement was not affected by age, but patients who had fever, hepatosplenomegaly, positive blood culture for *Brucella* spp. and patients with elevated liver transaminase had higher rates of hematological involvement in brucellosis.

Worldwide incidence of brucellosis in endemic countries varies from <0.01 to >200 per 100000 population.[6,7] In 2017, 381 confirmed cases of human brucellosis were reported in 20 European Union (EU) countries, with a rate of 0.10 cases per 100.000 population. The highest numbers of confirmed cases were reported in Greece, Italy and Spain that accounted for 67.2% of all confirmed cases in EU countries in that year.[8] In Turkey, brucellosis remains a major public health issue, because the majority of people live in rural areas and they are engaged in animal husbandry.[1] According to the Turkish Public Health Institution data, brucellosis affects 5.000 to 10.000 people each year and causes significant morbidity.[9] It has been reported that brucellosis often affects children aged 5 to 15 years of age in different pediatric studies.[1,10,11] A study conducted on 496 children with brucellosis in Eastern Turkey, showed that patients' age ranged from 1-16 years with a mean age of 10.0±3.95 years. Half of the children were over 10 years of age and the male/female ratio was 1.5.[12] In an another study including children with brucellosis living in central Blacksea region, 80.8% of patients were male and mean age was 11 years (range, 2-17 years).[11] In the present study male gender dominance and mean age of patients were similar with those reported in previous pediatric studies.

In endemic areas, it is known that consumption of raw milk and dairy products is the main source for childhood brucellosis. Direct contact with infected animal is a possible acquision route of infection in older children whose families are engaged in animal husbandry.[1,13] The majority of our patients had a history for consumption of unpasteurized milk, suggesting that this was the most common route of acquisition in this setting. Although human to human transmission is rare, cases of neonatal infection have raised the possibility of transplacental transmission. Furthermore, breastfed infants whose mothers have not been treated adequately might have been infected with *Brucella* spp. via human milk.[14,15] We thought that one of our patients who was a preterm neonate had acquired brucellosis through transplacental route. Furthermore, there another patient acquired brucellosis via breast feeding in our series.

Brusellosis in pediatric patients may have a wide variety of nonspecific clinical presentations. Patients may present with fever, sweats, malaise, anorexia, weight loss, arthralgias, myalgias, headache, and abdominal pain.[4,11,16,17] In a large study including 496 children (79.8% male), the most common symptoms were reported as arthralgia (46.2%), fever (32.1%) and abdominal pain (17.1%) and the most common physical examination findings were arthritis (10.1%), splenomegaly (2.2%) and hepatomegaly (1.8%), respectively.[12] In a study from China, 88 children and 354 adult patients with male predominance were included. The authors demonstrated that fever was the most comon symptom in both children and adults (82.9% vs 61.5%, respectively), followed by joint pain, fatigue, anorexia and low back pain.[10] In our study, as reported in previous studies, the most common symptoms were arthralgia and fever and the most common physical examination findings were hepatomegaly and arthritis.

In the course of childhood brucellosis hematological complications are well known. Mild anemia and leukopenia have been reported mostly during the course of acute brucellosis.[1,2,4,17] A comprehensive study including children living in an endemic area for brucellosis in Turkey analysed the hematologic manifestations of 622 patients. Hematologic involvement was observed in 292 patients (46.9%). The most common hematologic involvement was anemia (28.6%), followed by thrombocytopenia (16%) and leukopenia [13.9% (neutropenia 8%, lymphopenia 8.8%)]. Pancytopenia was observed in 7.7% of patients.[1] The incidence of anemia has been reported as 13.3%-55% in different pediatric series.[1,12,18-20] In the present study anemia was the most common hemeatologic finding of brucellosis. We used hemoglobin levels determined for age to be able to make an objective evaluation when describing hematological findings like most other studies. In a pediatric study evaluating the hematological findings of brucellosis, cytopenia at least in one blood cell lineage detected in 41.9% of the patients, leukopenia in 28.2%, thrombocytopenia in 14.5%, anemia in 13.3%, and pancytopenia in 13.3%. Anemia had not been found as the most common hematological finding of brucellosis in this study in contrast to other pediatric studies. Authors thought that, this difference may be a result of choosing relatively low cut-off for hemoglobin levels of 10 mg/dl in order to minimize the anemia cases misrelated to brucellosis.[18] Moderate to severe leukopenia and thrombocytopenia as well as normal leukocyte and thrombocyte counts in patients with brucellosis were reported.[1,12,18,19,21] On the contrary of leukopenia predominance in previous reports, in a prospective case-control study including 100 brucellosis patients and 100 healthy individuals, the authors found that WBC, CRP and neutrophil counts were significantly higher in the brucellosis group. As a result of this study, they concluded that the most significant laboratory findings of brucellosis were increased number of WBC, while decreased numbers of thrombocytes and lymphocytes.[22]

Pancytopenia and severe thrombocytopenia or isolated thrombocytopenia resulting in bleeding has rarely been reported in the course of brucellosis.[18,21,23] The pathogenesis of thrombocytopenia during brucellosis may be multifactorial such as; increased platelet clearance due to splenomegaly, the suppressive effect of brucellosis bacteremia on bone marrow, hemophagocytosis, and peripheral autoimmune destruction.[1,18,23] In a study that included five patients (2.6% of all) with isolated thrombocytopenia during the course of acute brucellosis, an examination of bone marrow aspirate had revealed increment of megakaryocytes in two of these patients that may also be seen in idiopathic thrombocytopenic purpura. Authors suggested that; the mechanisms of thrombocytopenia may be destruction of thrombocytes by antibodies against *Brucella* organisms which cross react with thrombocytes.[23] Whereas the pathogenesis of pancytopenia in brucellosis seems multifactorial, hypersplenism may be a possible explanation of pancytopenia in children infected with *Brucella spp*. In addition several possible mechanisms for pancytopenia such as hemophagocytosis (like that seen during the course of several infections including viral, bacterial, fungal and parasitic diseases), bone marrow hypoplasia, bone marrow granulomas, immune destruction, and the direct inhibitor effect of bacteria on bone marrow cells have been accused previously.[1,2,4,24] In a study from Turkey including children with brucellosis, pancytopenia had been found in 11 of the 52 patients (21%) as the initial manifestation of brucellosis. One of these patients had presented with the complaint of nose bleeding and two patients had presented with gingival bleeding. More than a half of patients had hepatosplenomegaly.[24] In a study including 146 children hospitalized due to brucellosis, 14 (9.6%) had presented with hematologic manifestations, nine of them had pancytopenia and five had immune thrombocytopenia. Bone marrow aspiration and biopsy of the patients with pancytopenia revealed hypercellularity or severe hemophagocytosis.[4] The present

study's findings for hematological involvement frequency was in agreement with those previous reports. The most common findings following anemia were leukopenia and thrombocytopenia while the least common finding was pancytopenia which was detected in only four patients, similar as previous reported studies. Hemophagocytosis in bone marrow aspirate was detected in one of the our patients who had pancytopenia. Other four patients with hemophagocytosis presented with hematologic abnormalities in two series.

A study evaluating 511 brucellosis episodes reported that 42% of patients had cytopenia in at least one series. The authors demonstrated that older age (10.49±4.81 vs. 9.25±4.89 years), fever (92% vs. 78%), positive blood culture (84% vs. 75%), and IgM ≥1:640 levels (50% vs. 39%) were associated with the presence of cytopenia. The authors suggested that presence of fever and positive blood culture are the component of acute disease and high rates of cytopenia during acute brucellosis is a common finding. It was postulated that *Brucella* organisms suppress cell production in the bone marrow during bacteremia, especially when the bacterial load is high.[18] Similary, a study of 69 children with brucellosis found a tendency to decrease platelet count in patients with bacteremic disease.[2] In an another study including 123 brucellosis patients aged 13-73 years (60 patients with *Brucella* spp. bacteremia and 63 patients without bacteremia) revealed that, bacteremic patients presented with fever and chills more than nonbacteremic patients. In addition a significant elevation of AST and ALT concentrations and higher leukopenia rates were detected in bacteremic patients.[25] On the contrary to previous reports[18] we did not find any correlation between hematological involvement and age of patients, however in line with other previous reports[2,18,25] we found a correlation between hematological involvement and presence of bactremia, fever, hepatosplenomegaly and elevated liver transaminase levels.

It is well known that, clinical and hematological improvement usually occurs within 2 to 3 weeks after the initiation of appropriate antimicrobial therapy.[2,4] In addition, IVIg may be reserved as an emergent treatment for patients presented with hemophagocytosis or patients presented with severe bleeding symptoms and had symptoms of idiopathic thrombocytopenic purpura.[4] We prescribed IVIg in addition to antimicrobial therapy in a total of six patients who presented with hemophagocytosis in bone marrow, severe thrombocytopenia, and hemolytic anemia.

In conclusion; we postulated that brucellosis should be considered in the differential diagnosis of patients presenting with one of the findings including fever, hepatosplenomegaly, elevated liver transaminase and hematologic abnormality at least in one series especially in endemic regions like our country. Hematological involvement in at least one cell lineage was a common finding (43.4% of patients) regardless of age, especially in febrile, bacteremic patients and in patients who had hepatosplenomegaly and elevated liver enzymes. Anemia was the most common hematological abnormality, pancytopenia, severe thrombocytopenia and neutropenia were uncommon findings.

Ethical approval

This study was conducted in compliance with the ethical principles according to the Declaration of Helsinki, and it was approved by the Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital Institutional Review Board (Number: 2019/8).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: AK, FNÖ, AF; data collection: AK, SYD; analysis and interpretation of results: AK, AF, GT, TAT; draft manuscript preparation: AK, FNÖ, AF, TAT. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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