

Pediatric brucellosis in the central mediterranean region of Türkiye: Insights from a single-center experience

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ABSTRACT

Objective: We aimed to contribute to the literature by presenting the epidemiologic, clinical, and laboratory characteristics of pediatric patients with brucellosis followed up by our clinic.

Method: The medical records of patients aged 0-18 years who were followed up with a diagnosis of brucellosis in Gazi University Pediatric Infectious Diseases Clinic between 2010-2020 were retrospectively analyzed. The effect of demographic, clinical, and laboratory markers on diagnosis was investigated.

Results: The mean age was 162.0 ± 55.5 months. Of the 47 patients included in our study, 68% lived in rural areas. While 82.5% had a background of consuming raw milk and dairy products, 55% had experience in animal husbandry. Twenty-two patients had a family history of brucellosis. The most common symptoms were joint pain in 85%, malaise in 78%, and muscle pain in 42%. The most common associated findings were fever in 59%, joint stiffness in 23%, and splenomegaly in 17%. The decrease in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values and the increases in leukocytes, hemoglobin, and platelets before and after treatment were statistically significant ($p < 0.001$). Anemia was the most common in the patients, followed by neutropenia, thrombocytopenia, thrombocytosis, leukocytosis, and pancytopenia, respectively. Blood culture positivity was 12%. Of 47 patients with positive tube agglutination titer, Rose Bengal was positive in 80% and negative in 19%.

Conclusion: Brucellosis remains an important public health problem in Türkiye. Patients should be questioned in detail in the presence of fever, arthralgia, hepatosplenomegaly, and pancytopenia which presents with different clinical findings. Rose Bengal negativity, which is used as a screening test, should not mislead us in making a diagnosis in the presence of clinical suspicion. Tube agglutination tests should definitely be performed in patients with suspected brucellosis. In addition, changes in non-specific blood parameters such as CRP, ESR, leukocytes, hemoglobin, and platelets may be indicative for clinicians.

Keywords: Blood, brucellosis, childhood



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INTRODUCTION

Brucellosis is one of the most common zoonotic bacterial infections worldwide.¹ Brucellosis is endemic in the Mediterranean basin including Turkey, the Middle East, Central Asia, China, the Indian subcontinent, sub-Saharan Africa and Mexico, and parts of Central and South America. Worldwide, approximately 500,000 cases are reported annually.² According to the Turkish Ministry of Health reports, 9,818 cases were reported in 2008 and this number was last updated to 6,457 cases in 2017 (morbidity rate 7.99 per 100,000).³

Brucellosis, which is an important public health problem in Türkiye, is transmitted to humans mainly through the consumption of unpasteurized dairy products or contact with tissues of infected animals (cattle, sheep, goats, pigs) or inhalation of infected aerosolized droplets.⁴⁻⁶

The causative *Brucella* species are small gram-negative coco-bacilli. While six species can cause disease in animals, only four species (*B. abortus*, *B. melitensis*, *B. suis* and, less commonly, *B. canis*) cause disease in humans.^{3,5,6} Brucellosis is a systemic disease that can be very difficult to diagnose in children. Symptoms may be acute or insidious and are usually non-specific. Brucellosis typically presents with fever, malaise, night sweats, and joint pains.^{2,5} Physical examination findings are variable but non-specific; hepatomegaly, splenomegaly, and/or lymphadenopathy may be seen. Laboratory findings of brucellosis may include elevated transaminases and hematologic abnormalities, including anemia, leukopenia, or leukocytosis with relative lymphocytosis, and thrombocytopenia.^{2,6} Additionally, in endemic countries, *Brucella* spp. may be an important cause of occult bacteremia in children.⁶

Due to the insufficient number of reports and diagnostic difficulties, there are not many series of childhood brucellosis in the literature and there are few publications on this subject in Türkiye.^{7,8}

In this study, we aimed to contribute to the literature by presenting the epidemiologic, clinical, and laboratory characteristics of pediatric patients with brucellosis followed up in our clinic.

MATERIALS AND METHODS

In this study, a patient group consisting of 51 pediatric patients aged 0-18 years who were followed up with a diagnosis of brucellosis in Gazi University Pediatric Infectious Diseases Clinic between January 1, 2010 and January 1, 2020 were

accepted as the population and their files were retrospectively reviewed. Patients with a history of underlying comorbidity, organ involvement, complications, and incomplete medical records were excluded from the study. Patients' age, gender, risk factors for brucellosis (consumption of unpasteurized milk/dairy products, living in a rural area, and being engaged in animal husbandry), and family history of similar diseases were recorded. Patients were asked whether they had received treatment in an external center before they were referred to us. Admission complaints and physical examination findings, laboratory (complete blood count, liver function tests, C-reactive protein (CRP) and erythrocyte sedimentation rates (ESR), and microbiological tests were evaluated. Liver function tests, CRP, ESR, leukocyte, platelet, and hemoglobin values in the complete blood count were evaluated according to the age-specific normal values. In addition, the patients in our study were compared with regard to the laboratory parameters examined one day before the treatment and after the treatment. Blood cultures were performed using automated BACTEC (Becton Dickinson Diagnostic Instruments, Sparks, MD) and samples were kept for at least two weeks. The diagnosis of brucellosis was confirmed by a positive blood culture and/or a positive slide agglutination/STA (>1:160) test. SPSS version 25.0 (IBM Corp., Armonk, New York, USA) statistical software was used for data analysis. Categorical variables are presented as numbers and percentages, and numerical variables are presented as mean \pm standard deviation and median. The compatibility of the numerical variables with normal distribution was tested with the Kolmogorov-Smirnov test and the Mann-Whitney U test was used to evaluate the non-normally distributed data. The statistical significance level was accepted as $p < 0.05$. This study was approved by Gazi University Clinical Research Ethics Committee on 09/01/2023.

RESULTS

Of the 47 patients included in the study, 41 (87.2%) were male, 6 (12.8%) were female and the mean age was 162.0 ± 55.5 months. Of the 47 patients with brucellosis, 32 (68%) lived in rural areas and 26 (55%) had a history of animal husbandry. In our study, 27 (82.5%) patients had a history of consuming raw milk and dairy products and 22 (46%) patients had a history of active brucellosis in their relatives. Twenty-seven of these patients had received irregular treatment in external centers before being referred to us.

Joint pain (85%), malaise (78%), and myalgia (42%) were the most common symptoms, while fever (59%), limitation of movement in the joint (23%), and splenomegaly (17%) were the most common associated findings (Table 1).

Table 1. Clinical Characteristics of Pediatric Patients Diagnosed with Brucella

Symptoms (n= 47)	
Arthralgia (+), n (%)	40 (85.1)
Malaise (+), n (%)	37 (78.7)
Myalgia (+), n (%)	20 (42.6)
Night sweats (+), n (%)	19 (40.4)
Weight loss (+), n (%)	18 (38.3)
Headache (+), n (%)	16 (34.0)
Abdominal pain (+), n (%)	15 (31.9)
Vomiting (+), n (%)	14 (29.8)
Skin rash (+), n (%)	11 (23.4)
Findings (n= 47)	
Fever $\geq 38^{\circ}\text{C}$ (+), n (%)	28 (59.6)
Limitation of joint movement (+), n (%)	11 (23.4)
Splenomegaly (+), n (%)	8 (17.0)
Lymphadenopathy (+), n (%)	6 (12.8)
Increase in joint temperature (+), n (%)	4 (8.5)
Joint swelling (+), n (%)	3 (6.4)
Hepatomegaly (+), n (%)	2 (4.3)

Anemia was the most common in the patients, followed by neutropenia, thrombocytopenia, thrombocytosis, leukocytosis, and pancytopenia, respectively (Table 2).

While the decrease in ESR and CRP values after treatment was statistically significant ($p < 0.001$), a statistically significant increase was also found in leukocyte, hemoglobin (Hb), and platelet (plt) values after treatment ($p < 0.001$). The change in liver transaminase levels was not statistically significant ($p > 0.05$) (Table 3).

Blood culture positivity was found in 6 (12%) cases. While the Rose Bengal screening test was positive in 38 (80%) of 47 cases with a positive brucella tube agglutination titer, it was remarkable that the test was negative in 9 (19%) cases.

DISCUSSION

Brucellosis is a bacterial zoonotic infection that has not yet been eradicated worldwide and is observed at a higher rate, especially in the Eastern and Southeastern Anatolia regions in Türkiye.^{2,3} Every year, 500 thousand new cases of brucellosis occur in the world, and the incidence rate in Türkiye range between 1% and 26.7% depending on the geographical region.^{2,9}

Table 2. Laboratory Characteristics of Pediatric Patients Diagnosed with Brucella at the Time of Diagnosis

Anemia, n (%)	8 (17.0)
Leukocytosis, n (%)	2 (4.3)
Leukopenia, n (%)	8 (17.0)
Thrombocytopenia, n (%)	4 (8.5)
Thrombocytosis, n (%)	3 (6.9)
Pancytopenia, n (%)	1 (2.1)
Increased ESR, n (%)	15 (31.9)
Increased CRP, n (%)	21 (44.7)
Increased transaminase, n (%)	9 (19.1)

Although pediatric brucellosis is seen in all ages and sexes in Türkiye, in case series written on this subject, it is more common in the male sex and the mean age is reported to be between 5-11 years.^{7,10} The mean age and gender results obtained in our study were found to be compatible with the literature.

In countries where the disease is endemic, such as Türkiye, the main mode of transmission is the consumption of raw milk and dairy products, while in developed countries, transmission by inhalation or direct contact with an infected animal is more prominent.^{2,5,6}

Studies conducted in Türkiye have reported a history of consumption of raw milk and dairy products ranging between 21% and 80%.^{10,11} In our study, a significant proportion of participants reported a history of consuming raw milk and dairy products. In a study of adult cases from Türkiye, the rate of animal contact was 44%, while this rate was 55.3% in our study.¹² This may be due to the fact that 68.1% of the cases lived in rural areas.

Since the most common mode of transmission is through the consumption of infected food, more than one case of brucellosis may be found in the same family. It is therefore very important to perform a family screening to evaluate other family members for symptoms and findings when brucellosis is diagnosed. In our study, about half of the patients had a family history of brucellosis, and this rate is supported by similar results in other pediatric studies.¹³

In brucellosis, the presence of very different symptoms and signs, which are non-specific and can be confused with many other diseases, may lead to delays in diagnosis and treatment.² In our study, the most common symptom was joint pain, followed by fatigue, muscle pain, and night sweats. The most common findings were fever, limitation of movement in the

Table 3. Comparison of Laboratory Characteristics of Pediatric Patients with Brucella at Diagnosis and After Treatment			
Laboratory Features	At Diagnosis	After Treatment	p value
Leukocyte (x10 ³ /mm ³) (n=47) Mean ± SD	6.23 ± 1.55	6.86 ± 1.98	p<0.001
Median	5.80	6.43	
Range (min- max)	4.10 – 12.30	4.00 – 13.94	
Platelets (x10 ³ /mm ³) (n=47) Mean ± SD	2.61 ± 0.59	2.67 ± 0.66	p<0.001
Median	2.56	2.83	
Range (min- max)	1.45 – 3.89	1.24 – 4.00	
Hemoglobin (%) (n=47) Mean ± SD	12.58 ± 1.01	12.88 ± 1.60	p<0.001
Median	12.80	13.20	
Range (min- max)	9.5 – 14.2	9.7 – 14.7	
ESH (mm/h) (n= 47) Mean ± SD	23.11 ± 18.80	10.47 ± 6.76	p<0.001
Median	6.43	10.00	
Range (min- max)	2 – 84	2 – 26	
CRP (mg/L) (n= 47) Mean ± SD	27.28 ± 31.01	5.40 ± 4.57	p<0.001
Median	13.30	4.51	
Range (min- max)	1 – 125	1 – 25	
ALT (U/L) (n= 47) Mean ± SD	46.02 ± 41.40	26.66 ± 19.91	p=0.498
Median	27	20	
Range (min- max)	6 – 180	6 – 90	
AST (U/L) (n= 47) Mean ± SD	45.17 ± 30.70	28.45 ± 10.06	p=0.210
Median	34	28	
Range (min- max)	14 – 169	10 – 52	
Culture growth (+) (n= 47)	6 (12%)		

joint, splenomegaly, and lymphadenopathy. The symptoms and findings in our study were similar to those reported in the case series related to this subject in the literature.¹⁴⁻¹⁶

Although hematologic involvement is frequently observed in brucellosis, it is not diagnostic and usually does not require treatment.^{2,17} Hematologic disorders including anemia, leukopenia, thrombocytopenia, and pancytopenia can be observed in childhood brucellosis.^{2,6,16} In our study, the most commonly observed hematologic disorders were anemia and leukopenia (17%).

Thrombocytopenia was found in 8.5%, thrombocytosis in 6.9%, and pancytopenia in 2.1%. Our findings were similar to those in other studies on this subject.

Acute phase reactants are supportive rather than diagnostic in brucellosis cases. They may be high or normal.^{2,6,17} In our study, a considerable number of participants had elevated levels of

ESR, while a significant portion had increased levels of CRP. In our study, the decrease in ESR and CRP values before and after treatment was statistically significant (p<0.001).

This is associated with the expected decrease in inflammatory markers following the treatment. The increase in leukocyte, hemoglobin (Hb), and platelet (plt) values after treatment was statistically significant (p<0.001) (Table 3).

The liver is often affected by brucellosis. Liver enzymes generally tend to increase in this disease. Some studies reported transaminase elevation in 18.3-55%.^{7,14,18} In our study, transaminase elevation was found in approximately one-fifth of the patients. These findings were compatible with the literature. In addition, no significant statistical change was found in liver transaminase levels with treatment in our study (p>0.05).

Brucellosis is diagnosed on the basis of positive serological tests and/or the production of the agent in culture.^{2,5,6} Serologic

tests are very important for diagnosis. For this purpose, the tube agglutination test (Wright), slide agglutination test (Rose Bengal), complement-fixation test, and ELISA are used.^{2,5,6} The most commonly used test in Türkiye is the Wright test.^{14,15} Although a single titer is not diagnostic, it is found to be 1/160 and above in most patients with active infection.^{2,6,17} In our patients, antibody titers ranged between 1/160 and 1/320. In a study on Rose Bengal agglutination test, which is one of the serologic tests with a short turnaround time used for screening purposes Türkiye, sensitivity and specificity were found to be 87% and 100%, respectively.² In our study, the fact that the Wright agglutination test result was positive in nine patients with a negative Rose Bengal test revealed the importance of performing further investigation in cases of clinical suspicion.

The definitive diagnosis in patients with brucellosis is made by producing the causative agent.^{2,17} In various studies reported outside our country, the growth rate of the causative agent in blood culture in children with brucellosis varied between 23.5% and 57%.^{19,20} In a study reported from our country, the rate of growth in blood culture was reported to be 72%.¹⁵ In our study, the growth rate in blood culture was found to be 12%. This growth rate was lower than in previous studies, which we interpreted as being related to the inadequate and irregular drug use history of the patients before they presented to our center.

Our study had some limitations. Since our study was a single-center study, the number of cases was small, making it difficult to attribute the data to the general population. In addition, the fact that it was a retrospective study and that the data were collected by scanning the medical records and computer database was another limiting factor. Not all data were accessible due to technical problems in the database. Prospective and multicenter studies on the subject are important and necessary to provide up-to-date clinical and surveillance data.

CONCLUSION

Brucella can clinically mimic many diseases and may present with various non-specific signs and symptoms. This is directly related to delays in diagnosis and treatment. In Türkiye, it is important to take a family history in terms of brucellosis and to ask about suspicious food consumption for early diagnosis in patients presenting with fever, hepatosplenomegaly, bicytopenia, or elevated transaminases. In cases with brucellosis, it is usually not possible to produce the causative agent in culture, and Rose Bengal test negativity, which is used as a screening test, should not mislead us in making a diagnosis in the presence of clinical suspicion. In addition to serologic tests, changes in non-specific blood parameters such as CRP, ESR, leukocytes, hemoglobin, and platelets may guide clinicians in treatment follow-up.

Ethical approval

This study has been approved by the Gazi University Clinical Research Ethics Committee (approval date 09.01.2023, number 11). Informed consent was not required because of the retrospective design.

Author contribution

Surgical and Medical Practices: EG, TBD, EYO, SHA, VM, NAÜ; Concept: EG, TBD, EYO, NKU, HT, AT; Design: EG, TBD, EYO, SHA, VM, NKU, HT, AT; Data Collection or Processing: EG, TBD, EYO, SHA, NKU, HT, AT; Analysis or Interpretation: EG, TBD, VM; Literature Search: EG, TBD, EYO, SHA, VM, NAÜ; Writing: EG. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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