



Retrospective Evaluation of Pediatric Patients Hospitalized with Brucellosis: Single Center Study in Istanbul

İstanbul'da Hastaneye Yatırılan Pediatrik Brusellozlu Hastaların Retrospektif Değerlendirmesi: Tek Merkezli Bir Çalışma

Ayşe Karaaslan¹, Ceren Çetin¹, Merve Akçay², Damla Beytorun², Nahide Haykır Zehir²,
 Yakup Çağ², Yasemin Akın²

¹Kartal Dr. Lütfi Kırdar City Hospital, Department of Pediatric Infectious Diseases, Istanbul, Turkey
²Kartal Dr. Lütfi Kırdar City Hospital, Department of Pediatrics, Istanbul, Turkey

Abstract

Aim: Brucellosis is a zoonotic disease and mainly develops as a result of consuming products of infected animals such as cattle, sheep and pigs.

Material and Method: Pediatric patients under the age of 18 who were hospitalized with a diagnosis of brucellosis in a third-level city hospital were included in the study. Serology titer $\geq 1:160$ and/or *Brucella* spp. in blood culture growth was determined as the diagnostic criterion for the diagnosis of brucellosis.

Results: Of the 35 pediatric patients diagnosed with brucellosis, 22 were boys and 13 were girls, and the average age was determined as 154.2 ± 53.1 months (25-214). Hospital admission complaints were determined in order of frequency as follows; joint pain (51.4%), fever (31.4%), headache (17.1%) and abdominal pain (5.2%). Eleven of the patients (31.4%) had polyarthralgia and 7 (20%) had monoarthralgia. The most common physical examination findings were hepatomegaly (48.6%) and splenomegaly (40%), respectively. Joint involvement was detected in 17.1% of the patients. Sacroiliac joint involvement was reported in 3 (8.6%) patients, ankle joint involvement in 2 (5.7%) patients, and knee joint involvement in 1 (2.9%) patient. Anemia (60%) was the most common hematological finding. The average hemoglobin value was determined as 12.5 ± 1.44 (10.2-15.9) g/dl. When patients are compared in terms of joint involvement; neutrophil count and treatment duration were found to be statistically higher in patients with joint involvement ($p < 0.05$).

Conclusion: Brucellosis is a zoonotic disease that is endemic in our country, affects all age groups, and can cause complications and relapses, and continues to be a serious public health problem for our country.

Keywords: Brucella, child, zoonotic disease

Öz

Amaç: Bruselloz, zoonotik bir hastalık olup, başlıca enfekte sığır, koyun ve domuz gibi hayvanların ürünlerinin tüketilmesi sonucu gelişir.

Gereç ve Yöntem: Üçüncü düzey bir şehir hastanesinde bruselloz tanısıyla hastaneye yatan 18 yaş altı çocuk hastalar çalışmaya dahil edildi. Seroloji titresinin $\geq 1:160$ olması ve/veya kan kültüründe *Brucella* spp. üremesi bruselloz tanısı için tanı kriteri olarak belirlendi.

Bulgular: 35 bruselloz tanılı çocuk hastanın 22'si erkek, 13'ü kız idi ve ortalama yaş 154.2 ± 53.1 ay (25-214) olarak belirlendi. Hastane başvuru şikayetleri sıklık sırasında göre şöyle belirlendi; eklem ağrısı (%51.4), ateş (%31.4), baş ağrısı (%17.1) ve karın ağrısı (%5.2). Hastaların 11'inde (%31.4) poliartralji, 7'sinde (%20) ise monoartralji şikayeti mevcut idi. En sık saptanan fizik muayene bulguları sırasıyla hepatomegali (%48.6) ve splenomegali (%40) olarak belirlendi. Hastaların %17.1'inde eklem tutulumu saptandı. 3 (%8.6) hastada sakroiliak eklem, 2 (%5.7) hastada ayak bileği eklemi, 1 (%2.9) hastada ise diz eklem tutulumu raporlandı. Anemi (%60) en sık saptanan hematolojik bulgu idi. Hemoglobinin değeri ortalama 12.5 ± 1.44 (10.2-15.9) g/dl olarak saptandı. Hastalar eklem tutulumu açısından karşılaştırıldığında; eklem tutulumu olan hastalarda nötrofil sayısı ve tedavi süresi istatistiksel olarak daha yüksek bulundu ($p < 0.05$).

Sonuç: Bruselloz ülkemizde endemik olan, tüm yaş gruplarını etkileyen, komplikasyon ve nökslere neden olabilen zoonotik bir hastalıktır ve ülkemiz için ciddi bir halk sağlığı sorunu olmaya devam etmektedir.

Anahtar Kelimeler: Brucella, çocuk, zoonotik hastalık



INTRODUCTION

Brucellosis, also known as "Mediterranean fever" or "Malta fever", is a most common zoonotic infection transmitted to humans by consuming the products of infected cattle, sheep, pigs and some other animals.^[1] Several species of the *Brucella* genus cause this disease, four *Brucella* types known as *Brucella abortus* (*B. abortus*), *B. melitensis*, *B. suis* and *B. canis* cause disease in humans, and *B. melitensis* and *B. suis* are known to be more virulent subspecies.^[2] In this infectious disease, which usually has an incubation period of two to four weeks, clinical findings can vary in a wide range, but it can be said that the characteristic findings are fever, fatigue and arthralgia.^[3] One of the most important and frightening features of *Brucella* disease is that it can affect all organs. The osteoarticular system is the most frequently involved system in brucellosis, followed by genitourinary system involvement.^[4,5] Although less frequently, neurological involvement, hematological involvement, ocular involvement, skin involvement, cardiovascular involvement and pulmonary involvement can also be observed. Although brucellosis is a disease that can be seen at any age, 20-30% of cases are diagnosed in childhood.^[6,7]

Brucellosis is endemic in Mediterranean basin countries, China, the Middle East, the Indian subcontinent, sub-Saharan Africa and parts of South America and 500,000 cases are reported worldwide every year.^[1,8] Our country, Turkey, is an endemic country for brucellosis. According to the statistics of the General Directorate of Public Health of our country, the number of cases, which was 4173 in 2015, was reported as 6457 in 2017.^[9] Although it is more common in the eastern provinces of our country, where the animal husbandry profession is more common, cases are encountered in every province throughout the country due to the habit of eating village cheese. In this study, we aimed to present the general characteristics and treatment regimen of patients hospitalized with the diagnosis of brucellosis.

MATERIAL AND METHOD

The study was performed in a tertiary city hospital in Istanbul which has a capacity of 100-bed pediatric unit. Electronic medical records from May 2015 to May 2023 were retrospectively reviewed to identify patients aged between 1 month and 18 years who were diagnosed with brucellosis.

All patients were questioned in terms of suspicious food consumption. Clinical and physical examination findings consistent with the disease and positive serology titer of $\geq 1:160$ or patients with a positive blood culture for *Brucella* spp. was diagnosed with brucellosis. A positive blood culture in an asymptomatic patient was also accepted as diagnostic.^[10,11] Some patients also underwent related serological tests such as ELISA.

Although fever, night sweats, fatigue, and arthralgia were considered the main clinical findings, symptoms such as

weight loss, headache, abdominal pain, back pain, and depression were accepted as clinical findings consistent with the disease. Findings such as hepatomegaly, splenomegaly, lymphadenopathy, and pallor were also accepted as physical examination findings compatible with the disease.

Patients were identified through the department's archived patient files, and patients' information including age, sex, clinical findings, laboratory findings [(white blood cell; WBC), hemoglobin count, platelet count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT)], microbiological findings (blood culture), radiological findings (ultrasonography), treatment strategies and duration of hospital stay were collected. Echocardiography was performed in all patients with the diagnosis of brucellosis.

This study was approved by the Medical Research Ethics Committee of our institution (Date: 28.08.2023 Report Number:2023/514/256/4).

Normally distributed quantitative variables were expressed as mean \pm standard deviation, whereas non-normally distributed quantitative variables were expressed as median with interquartile ranges (IQR). Chi square test was used for comparing categorical variables. Mann-Whitney U test was used to compare two groups of non-normally distributed data. Student t-test was used to compare two groups of normally distributed data. All analyses were conducted using SPSS 25 software (IBM SPSS Statistics, New York), and $p < 0.05$ indicated a statistically significant difference.

RESULTS

Thirty-five children diagnosed with brucellosis were included in the study. 22 of the patients were male and 13 were female (male/female: 1.7) and the average age was 154.2 \pm 53.1 months (25-214). 94.2% of the patients had a history of consumption of raw milk and its products. All the patients were live in Istanbul, and there was no history of travel to other provinces from an epidemiological perspective.

The most common presenting symptom was arthralgia (51.4%), followed by fever (31.4%), headache (17.1%) and abdominal pain (5.2%). 11 (31.4%) of the patients with joint pain presented with polyarthralgia and 7 (20%) presented with monoarthralgia. When physical examination findings are examined; the most common finding was hepatomegaly (48.6%), while splenomegaly (40%) was the second most common finding. Joint involvement was detected in 17.1% of the patients, and when evaluated in terms of the sites of involvement, it was determined that the sacroiliac joint was involved in 3 (8.6%) patients, the ankle joint was involved in 2 (5.7%) patients, and the knee joint was involved in 1 (2.9%) patient.

Blood cultures of all patients were taken and *Brucella* spp. was detected in the blood cultures of 3 (8.6%) patients. While 28

(80%) patients aged over 8 years were given doxycycline and rifampicin oral treatments, 7 (20%) patients under 8 years of age were given trimethoprim-sulfometaxazole and rifampicin oral treatment combinations. Additionally, 10 (28.5%) patients received triple combination therapy with aminoglycosides. Although the treatment duration was determined as a minimum of six weeks, the treatment duration of patients with joint involvement was planned to be at least 3 months and was decided on a patient-by-patient basis.

The mean WBC count was $7440.29 \pm 2068.2/\text{mm}^3$ (min-max: 3000-12300), the mean ANC was $3705.4 \pm 1676.1/\text{mm}^3$ (min-max: 1000-8320), the mean platelet count was $274834 \pm 111932.4/\text{mm}^3$ (min-max: 2000-504000), and the median CRP was 2.5 mg/dL (IQR: 0.66-4.6, min-max: 0.1-50). The median erythrocyte sedimentation rate (ESR) was 11 mm/h (IQR: 4-20, min-max: 0-121). Anemia was detected in 60% of the patients and the average hemoglobin value was determined as 12.5 ± 1.44 (10.2-15.9) g/dl.

The median alanine aminotransferase (ALT) was 19 (IQR: 10-31, min-max: 6-174) and the median aspartate aminotransferase (AST) was 28 (IQR: 19-39, min-max: 12-142). Demographic and clinical characteristics of patients are shown in **Table 1**.

Sex	Male	22 (62.9)
	Female	13 (37.1)
Age (month) mean \pm SD (min-max)		154.2 \pm 53.1 (25-214)
Age distribution	<8 years	7 (20)
	\geq 8 years	28 (80)
Symptoms	Arthralgia	7 (20)
	Monoarthralgia	7 (20)
	Polyarthralgia	11 (31.4)
	Fever	11 (31.4)
	Headache	6 (17.1)
	Abdominal pain	2 (5.7)
Hepatomegaly		17 (48.6)
Splenomegaly		14 (40)
Joint involvement	Sacroiliac	3 (8.6)
	Ankle	2 (5.7)
	Knee	1 (2.9)
Lymphadenopathy		1 (2.9)

Echocardiography was performed in all patients and no cardiac involvement was detected in any patient. The mean hospitalization duration was 57.71 ± 28.6 days (min-max: 42-180 days). None of the patients died, and clinical cure was achieved in all patients.

We also compared patients with joint involvement and patients without joint involvement. The neutrophil count and treatment duration were found to be higher in patients with joint involvement than in those without joint involvement ($p < 0.05$). AST and ALT values were found to be higher in patients without joint involvement ($p < 0.05$). **Table 2** shows the comparison of patients with and without joint involvement.

The prognoses of the patients were generally favorable, with all patients achieving clinical cure and no deaths reported. Additionally, no patients experienced any drug side effects.

DISCUSSION

Brucellosis is a zoonotic disease that is endemic in our country, affects all age groups, and can cause complications and relapses, and continues to be a serious public health problem for our country. The main routes of transmission are the consumption of raw milk or dairy products of the infected animal, but it can also occur as a result of contact with the secretions of the infected animal, such as blood or urine.^[3] In our study, the main transmission route was found to be consumption of unpasteurized milk and dairy products such as yoghurt and cheese. In the study conducted by Tanir et al. with 90 pediatric patients with a diagnosis of brucellosis in our country, the most common mode of transmission was found to be the consumption of contaminated milk and dairy products, similar to our study.^[12] However, in a meta-analysis of 68 studies in China, it was reported that 79.4% of brucellosis was transmitted as a result of contact with sick animals.^[13] In a study conducted with pediatric patients diagnosed with brucellosis in Chicago, USA, where brucellosis is partially less problematic, consumption of raw milk and unpasteurized dairy products was found to be the cause of transmission at a rate of 76%.^[14]

Table 2. Comparison of patients with and without joint involvement

	Patients with joint involvement (n=6)	Patients without joint involvement (n=29)	p
Age (month) (median) (IQR)	185.5 (145-196.5)	169,00 (105.5-198.0)	0.431
Hb (g/dl) (Median) (IQR)	11.4 (11.0-13.5)	12.5 (11.6-13.4)	0.324
WBC (/mm ³) (Median) (IQR)	8555 (7080-9917)	7400 (5750-8490)	0.149
Lymphocyte (/mm ³) (Median) (IQR)	2245 (2005-3807)	2880 (2025-3835)	0.555
Neutrophil (/mm ³) (Median) (IQR)	5885 (3415-6420)	3300 (2375-4040)	0.026
Platelet (/mm ³) (Median) (IQR)	324000 (239750-374250)	273000 (201000-333000)	0.229
CRP (Median) (IQR)	1.34 (0.24-28.32)	2.98 (0.68-4.63)	0.710
ALT (U/L) (Median) (IQR)	9.5 (4.5-11.5)	21 (15-37)	0.003
AST (U/L) (Median) (IQR)	16.5 (13.5-23.5)	30 (20.5-41.5)	0.010
ESR (mm/h) (Median) (IQR)	23 (3,5-54,2)	10 (3,5-18)	0.188
Treatment duration (days) (Median) (IQR)	77 (60,7-112,2)	42 (42-52,5)	0.001

Hb: Hemoglobin; WBC: White Blood Cell; CRP: C-reactive protein; ALT: Alanine transaminase; AST: Aspartate transaminase; ESR: Erythrocyte sedimentation rate

In our study, although the disease was seen in both genders, it was observed that it was more common in male sex. The male/female ratio was determined as 1.7. In accordance with our study, in one of the most comprehensive studies conducted in our country, 189 pediatric patients with brucellosis were examined over a 16-year period and it was observed that 61.4% of the cases were male patients.^[15] Similarly, in another comprehensive study conducted with 212 pediatric patients diagnosed with brucellosis between 2005 and 2018 in our country, Kaman et al. reported that 59.9% of the cases were male.^[7] In a study conducted in Europe examining both children and adults diagnosed with brucellosis, it was shown that both genders were affected by the disease at almost equal rates (51% male).^[16]

In the study conducted by Özdem et al. in our country and published in 2022, the most common symptoms in 189 pediatric patients with brucellosis were determined as arthralgia (71.4%), fever (59.2%), weight loss (23%), and night sweats (14.3%). In the same study, fever (23%), hepatomegaly (19%), arthritis (17%), splenomegaly (14%) and lymphadenopathy (6%) were reported as the most common clinical findings, respectively.^[15] When we examine different geographical regions, it is seen that there are similar findings. In a study conducted in 246 pediatric patients diagnosed with brucellosis in Europe (Bosnia and Herzegovina) between 2000 and 2013, the most common clinical findings were reported as fever (78.86%) and joint pain (64.22%).^[16] In a study by Logan et al. in the United States, the most common findings in pediatric patients with brucellosis were fever (95%), anorexia (48%), fatigue (33%), chills (24%), arthralgia (24%), and weight loss (24%) was reported.^[14] Similarly, in a study conducted by Madut et al. in Africa examining pediatric and adult patients with brucellosis, fever and headache were determined as the most common findings, and shivering, fatigue, joint pains and night sweats were reported as other observed findings.^[17] Similarly, in our study, the most common presenting symptom was joint pain (51.4%), followed by fever (31.4%), headache (17.1%) and abdominal pain (5.2%). When physical examination findings are examined; the most common finding was hepatomegaly (48.6%), while splenomegaly (40%) was the second most common finding.

In a study examining 408 patients with brucellosis in Germany between 2006 and 2018, *B. melitensis* was the most commonly isolated species (91%), followed by *B. abortus* (8.1%) and *B. suis* (0.5%).^[18] In the articles published by Alshaalan et al., it was reported that the most common species causing brucellosis in Saudi Arabia and surrounding countries was *B. melitensis*, and the second most common species was *B. abortus*.^[19] In our study, we had patients with growth in blood culture, but we could not type them.

In our study, anemia was found to be the most common hematological finding. The most comprehensive study on pediatric patients diagnosed with brucellosis was conducted in the city of Van, located in the east of our country, and

Parlak et al. shared the data of 496 patients and anemia (20.4%), thrombocytopenia (15.5%), and leukopenia (12.1%) were reported as the most common hematological findings, respectively. In the same study, elevation of lactate dehydrogenase was found in 63.1% of the patients, and the acute phase values of C-reactive protein and erythrocyte sedimentation rate were found to be high by 58.7% and 55.2%, respectively.^[20] In a study conducted in Iran, the data of 100 patients with a definitive diagnosis of brucellosis were examined, and it was determined that neutrophil counts were higher in patients diagnosed with brucellosis than in the control group.^[21] In the study which Balin et al. examined the importance of hematological parameters in the diagnosis of osteoarticular brucellosis, they showed that neutrophil numbers were higher in brucellosis cases with osteoarticular involvement than in the control group.^[22] In our study, elevated CRP was detected in 22.9% of our patients and the neutrophil count was found to be higher in patients with joint involvement than in those without joint involvement. We think that these results can be considered normal since joint involvement is considered to be a more complicated condition of the disease. On the other hand, although liver enzymes such as AST and ALT were within the normal range, they were found to be higher in patients without joint involvement. Since liver enzymes were within the normal range, although there was a statistically significant difference between the two groups, we did not consider this as liver involvement.

In a study conducted in our country and investigating the complications of 283 patients including both pediatric and adult patients with brucellosis, the most common complication was found to be osteoarticular system involvement with a rate of 69%, and the most frequently involved joint was reported as the sacroiliac joint.^[23] On the other hand, in the study of Akkoç and Tekerek in which they examined 185 pediatric patients with brucellosis, hip joint involvement was determined as the most common joint involvement.^[24] In the study of Fanni et al. with Iranian children diagnosed with brucellosis, the most frequently affected joints were hip and knee, followed by elbow, wrist, ankle, and sacroiliac joints, respectively.^[25] In our study, joint involvement was detected in 17.1% of the patients, and when evaluated in terms of the sites of involvement, it was determined that the sacroiliac joint was involved in 3 (8.6%) patients, the ankle joint was involved in 2 (5.7%) patients, and the knee joint was involved in 1 (2.9%) patient.

In uncomplicated brucellosis cases, the treatment duration is generally 6 weeks. The main treatment regimen used in children under eight years of age includes the combined oral use of trimethoprim-sulfametaxazole and rifampin drugs. In children older than eight years of age, combined oral use of doxycycline and rifampin drugs is the main treatment method, but combined treatment regimens with doxycycline and aminoglycosides (amikacin or streptomycin) can also be applied instead of rifampin.^[4,10,26] The optimal

treatment protocol in cases of brucellosis with osteoarticular involvement is not clear, but in general, triple combination therapy of doxycycline (TMP-SMX instead of doxycycline in children younger than 8 years of age), rifampin and aminoglycoside (amikacin or streptomycin) is recommended for pediatric patients.^[27,28] The treatment duration is recommended as a minimum of 12 weeks.^[29] Although we treat all our patients with joint involvement for a minimum of 12 weeks, we have also had cases where treatment times have been extended for up to 6 months on a case-by-case basis. In our study, we showed that statistically the treatment duration was longer in our patients with joint involvement.

Although the limitation here is that the study was absence of long-term follow-up data to provide data on possible relapses, strength of our study is that clinical and laboratory findings were comprehensively evaluated in pediatric brucellosis cases with detailed data obtained from a single center.

CONCLUSION

Brucellosis is a zoonotic disease that we see in our country due to the continued consumption of raw milk and its products. It continues to be an important public health problem because it causes osteoarticular involvement and requires long-term treatment. It should be kept in mind that the disease can be prevented by simple methods such as health inspection of animals and pasteurization.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Medical Research Ethics Committee of our institution (Ethics Committee Name: University of Health Sciences, Kartal Dr. Lütfi Kırdar City Hospital Medical Research Ethics Committee Date: 28.08.2023 Report Number: 2023/514/256/4).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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REFERENCES

- Pappas G, Papadimitriou P, Akritidis N, Christou L, Tsianos EV. The new global map of human brucellosis. *Lancet Infect Dis.* 2006;6(2):91-9.
- Troy SB, Rickman LS, Davis CE. Brucellosis in San Diego: epidemiology and species-related differences in acute clinical presentations. *Medicine (Baltimore).* 2005;84(3):174-87.
- Pappas G, Akritidis N, Bosilkovski M, Tsianos E. Brucellosis. *N Engl J Med.* 2005;2;352(22):2325-36.
- Bosilkovski M, Krteva L, Caparoska S, Dimzova M. Osteoarticular involvement in brucellosis: study of 196 cases in the Republic of Macedonia. *Croat Med J.* 2004;45(6):727-33.
- Araj GF. Update on laboratory diagnosis of human brucellosis. *Int J Antimicrob Agents.* 2010;36 Suppl 1:S12-7.
- Young EJ. *Brucella species (Brucellosis)*. In: Long SS, Ficher M, Prober CG (eds). Principles and practice of pediatric infectious diseases (5th ed). Philadelphia, PA: Elsevier, 2018: 861-5.
- Kaman A, Öz FN, Fettah A, Durmuş SY, Teke TA, Tanır G. Clinicoepidemiological findings of childhood brucellosis in a tertiary care center in Central Anatolia: with the emphasis of hematological findings. *Turk J Pediatr.* 2022;64(1):10-8.
- Bosilkovski M, Dimzova M, Grozdanovski K. Natural history of brucellosis in an endemic region in different time periods. *Acta Clin Croat.* 2009;48(1):41-6.
- T.C. Ministry of Health, General Directorate of Public Health, Department of Zoonotic and Vector Borne Diseases. Brucellosis statistics. <https://hsgmdstek.saglik.gov.tr/tr/zoontikvektorel-bruselloz/istatistik>. Accessed August 14, 2023.
- Centers for Disease Control (CDC) Brucellosis Reference Guide 2017. <https://www.cdc.gov/brucellosis/pdf/brucellosi-reference-guide.pdf> (Accessed on May 23, 2019).
- Qasim SS, Alshuwaier K, Alosaimi MQ, et al. Brucellosis in Saudi Children: Presentation, Complications, and Treatment Outcome. *Cureus.* 2020;1;12(11):e11289.
- Tanır G, Tufekci SB, Tuygun N. Presentation, complications, and treatment outcome of brucellosis in Turkish children. *Pediatr Int.* 2009;51(1):114-9.
- 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;22;2018:5712920.
- Logan LK, Jacobs NM, McAuley JB, Weinstein RA, Anderson EJ. A multicenter retrospective study of childhood brucellosis in Chicago, Illinois from 1986 to 2008. *Int J Infect Dis.* 2011;15(12):e812-7.
- Özdem S, Tanır G, Öz FN, et al. Bacteremic and Nonbacteremic Brucellosis in Children in Turkey. *J Trop Pediatr.* 2022;7;68(1):fmab114.
- Ahmetagić S, Porobić Jahić H, Koluder N, et al. Brucellosis in children in Bosnia and Herzegovina in the period 2000 - 2013. *Med Glas (Zenica).* 2015;12(2):177-82.
- Madut NA, Nasinyama GW, Muma JB, et al. Prevalence of brucellosis among patients attending Wau Hospital, South Sudan. *PLoS One.* 2018;27;13(6):e0199315.
- Enkelmann J, Stark K, Faber M. Epidemiological trends of notified human brucellosis in Germany, 2006-2018. *Int J Infect Dis.* 2020;93:353-8.
- Mohammad A. Alshaalan, Sulaiman A. Alalola, Maha A. Almuneef, et al. AlShahrani, Sameera AlJohani, Brucellosis in children: Prevention, diagnosis and management guidelines for general pediatricians endorsed by the Saudi Pediatric Infectious Diseases Society (SPIDS). *International Journal of Pediatrics and Adolescent Medicine*, 2014;1:40-6.
- Parlak M, Akbayram S, Doğan M, et al. Clinical manifestations and laboratory findings of 496 children with brucellosis in Van, Turkey. *Pediatr Int.* 2015;57(4):586-9.
- Akya A, Bozogomid A, Ghadiri K, et al. Usefulness of Blood Parameters for Preliminary Diagnosis of Brucellosis. *J Blood Med.* 2020;30;11:107-13.
- Balin ŞÖ, Tartar AS, Akbulut A. The predictive role of haematological parameters in the diagnosis of osteoarticular brucellosis. *Afr Health Sci.* 2018;18(4):988-94.
- 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(1):33-44.
- Akkoc G, Tekerek S. Osteoarticular Involvement in Childhood Brucellosis: Evaluation of Clinical, Laboratory and Radiologic Features of 185 Cases. *Pediatr Infect Dis J.* 2023;1;42(5):381-8.

25. Fanni F, Shahbaznejad L, Pourakbari B, Mahmoudi S, Mamishi S. Clinical manifestations, laboratory findings, and therapeutic regimen in hospitalized children with brucellosis in an Iranian Referral Children Medical Centre. *J Health Popul Nutr.* 2013;31(2):218-22.
26. Ariza J, Bosilkovski M, Cascio A, et al. International Society of Chemotherapy; Institute of Continuing Medical Education of Ioannina. Perspectives for the treatment of brucellosis in the 21st century: the Ioannina recommendations. *PLoS Med.* 2007;4(12):e317.
27. Alp E, Doganay M. Current therapeutic strategy in spinal brucellosis. *Int J Infect Dis.* 2008;12(6):573-7.
28. Colmenero JD, Ruiz-Mesa JD, Plata A, et al. Clinical findings, therapeutic approach, and outcome of brucellar vertebral osteomyelitis. *Clin Infect Dis.* 2008;1;46(3):426-33.
29. Pappas G, Seitaridis S, Akritidis N, Tsianos E. Treatment of brucella spondylitis: lessons from an impossible meta-analysis and initial report of efficacy of a fluoroquinolone-containing regimen. *Int J Antimicrob Agents.* 2004;24(5):502-7.