Inflammatory marker comparison in childhood brucellosis: predicting osteoarticular involvement

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ABSTRACT

Background. Although the use of inflammatory markers in diagnosing *Brucella*-related complications has been the subject of research, studies on osteoarticular disease are insufficient, especially in children. This study aimed to compare inflammatory markers in children diagnosed with brucellosis, distinguishing between those with and without osteoarticular involvement (OI).

Methods. In this retrospective study, patients diagnosed with brucellosis from 1 month to 18 years of age were evaluated. Data collected included age, gender, OI, treatment duration, complete blood count, inflammatory markers including neutrophil-monocyte ratio (NMR), monocyte-lymphocyte ratio, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and *Brucella* serum agglutination test (SAT) results. OI was confirmed by MRI in symptomatic patients. The results of patients with and without OI were compared.

Results. The study included 38 patients, 23.7% having OI (8 with sacroiliitis and 1 with spondylitis). The median age of patients with OI was significantly higher than those without (p=0.037). All patients with OI (n = 9, 100%) had an SAT titer ≥ 1/640. Among patients without OI, 62% (n = 18) had an SAT titer ≥1/640. This difference was statistically significant (p = 0.028). Patients with OI had higher CRP levels (p=0.038) but similar ESR levels compared to those without. WBC levels were significantly lower in the group with OI (p=0.015). NMR was significantly higher in those with OI (p=0.012).

Conclusions. Lower WBC counts and higher CRP and NMR levels can predict OI in children with brucellosis at the time of admission. However, our findings should be validated through prospective studies involving larger patient groups.

Key words: brucellosis, osteoarticular brucellosis, neutrophile-to-monocyte ratio.

Brucellosis is one of the most prevalent zoonoses, causing some serious public health consequences.[1] Globally, approximately 500,000 human cases of brucellosis are reported annually.[2] According to European Center for Disease Prevention and Control (ECDC) data, the notification rate in Europe was 0.04 cases per 100,000 population.[3] Brucellosis is also endemic in Türkiye, with widespread disease throughout the country; however, the regions with the highest incidence are the southeast and east parts of the country. The Turkish Ministry of Health reported the incidence of brucellosis as 12.3 per 100,000 in 2019.[4]

Osteoarticular involvement (OI) is a widely reported manifestation in adults and is also the primary complication of brucellosis in children.[5,6] Brucellosis can lead to prolonged fever, hemophagocytic lymphohistiocytosis, endocarditis, meningitis, as well as peripheral arthritis, osteomyelitis, and, less commonly, severe osteoarticular complications such as spondylitis and sacroiliitis.[7] These complications in children not only cause school failure and economic burden due to hospitalization and long-term antibiotic use but also cause psychological problems along with loss of workforce, especially in adolescents. Therefore, early recognition of complications is essential.

Hematological parameters, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) are easily accessible markers commonly used in the follow-up of infections. Although the use of inflammatory markers in diagnosing brucellosis complications is a subject of research, studies on OI and the use of these markers to manage the disease remain limited, especially in children. This study aims to compare the inflammatory markers between patients with and without osteoarticular involvement.

Materials and Methods

The medical records of 48 patients (age range: 1 month to 18 years) diagnosed with brucellosis at the Department of Pediatrics and Pediatric Infectious Diseases in Konya City Hospital between July 2022 and January 2024 were retrospectively reviewed. After excluding the patients with incomplete demographic information, test results, or those transferred to another hospital for follow-up and treatment, the remaining 38 patients were enrolled. The following data were recorded for the patients: age, gender, presence of OI, presence of fever, treatment duration, complete blood count (including leukocyte, lymphocyte, neutrophil, monocyte, and platelet counts, mean platelet volume), inflammatory markers [neutrophil-to-monocyte ratio (NMR), monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), CRP, and ESR], and *Brucella* serum agglutination test (SAT) results at the time of admission. Serum samples were incubated with *Brucella abortus* antigen (*Brucella abortus* tube antigen supplied by the Public Health Institution of Türkiye, Ankara, Türkiye). *Brucella* antigen was evaluated for agglutinin particles for 24 h at 37°C, and samples with ≥ 1/160 were considered positive.

Definitions

OI was confirmed by magnetic resonance imaging (MRI) in patients with symptoms. Symptoms indicative of sacroiliitis included hip pain, inability to walk, and restriction of movement. Similarly, spinal pain, tenderness along the paravertebral region, and restricted movement were considered as symptoms of spondylitis.

The inflammatory markers of patients with and without OI were compared.

Statistical analysis

Statistical analysis was performed using SPSS statistical software (version 29.0.2.0; SPSS). Categorical variables were analyzed using relative frequencies, whereas numerical variables were analyzed using median or mean values (depending on whether they had a normal distribution). Categorical variables were compared using Pearson χ^2 and Fisher's exact tests. Numerical variables were compared using the t-test or the nonparametric Mann–Whitney U test. A $p < 0.05$ was considered to be statistically significant.

Ethical approval

The study was approved by the Necmettin Erbakan University Ethics Committee (date: 05.07.2024, number: 2024/5064)

Results

A total of 38 patients diagnosed with brucellosis were included in the study. Of the patients 65.8% were male and 34.2% female. The median age of the patients was 13 years (IQR: 9-15). Upon admission, 47.4% of the patients (18/38) presented with a fever. OI was proven by MRI in 23.7% (9/38) of the patients (sacroiliitis in 8 patients and spondylitis in 1 patient), while the other patients had no organ involvement. When comparing patients with and without OI, no significant gender difference was found (p=0.95). However, the mean age of patients with OI was significantly higher than those without (p=0.004).

From a diagnostic perspective, SAT titers ranged from 1/160 to 1/5120 among all patients. All patients with OI (n = 9, 100%) had an SAT titer ≥ 1/640. Among patients without OI, 62% (n = 18) had an SAT titer ≥1/640. This difference was statistically significant (p = 0.028). When comparing treatment durations, patients with OI received treatment significantly longer (median 6 weeks vs. 10,5 weeks, p=0.002).

Regarding symptoms and laboratory findings suggestive of an inflammatory process, there was no significant difference in fever between the two groups (p=0.18). The level of CRP was higher in patients with OI (p=0.039), while ESR was similar between the groups. Regarding hematologic parameters, white blood cell (WBC) count was significantly lower in the group with OI (p=0.013). Although the absolute lymphocyte, neutrophil, and monocyte counts were similar, NMR was significantly higher in the group with OI (p=0.012). The other markers, MLR, NLR, PLR, and MPV, were similar between the groups (Table I).

Table I. Demographics and laboratory findings of the patients (N=38).

	Patients with osteoarticular involvement	Patients without osteoarticular involvement	p-value
Number of patients (%)	9 (23.7%)	29 (76.3%)	
Age (year)*	14.6 ±2.2 (10-17)	11.1 ±4.4 (3-17)	0.004
Gender, n (%)			0.950
Male	6 (66.7%)	19 (65.5%)	
Female	3 (33.3%)	10 (34.5%)	
Treatment duration (week)**	11 (9-12)	6 (6-7)	0.002
SAT titer ≥1/640 (%)	100%	62%	0.028
WBC (/µL)**	5960 (5380-7390)	7480 (6485-9660)	0.013
ANC (/µL)**	2770 (2270-3900)	3570(2645-4740)	0.080
ALC (/µL)*	2478±663 (1170-3530)	3056 ±1374 (1040-6440)	0.235
AMC (/µL)**	500 (470-800)	550 (425-735)	0.893
NMR**	0.2 (0.2-0.2)	0.1 (0.1-0.2)	0.010
MLR*	0.2±0.1 (0.2-0.3)	0.2±0.2 (0.1-1)	0.786
NLR*	1.1±0.5 (0.3-1.9)	1.7±1.8 (0.1-8.7)	0.303
PLT (/µL)*	286888±63142 (193000-381000)	282586±92422 (78000-456000)	0.897
PLR**	120.9 (96.6-137.5)	101.4 (68.6-120.6)	0.277
MPV (fL)*	9.2±0.5 (8.5-9.9)	9.9±0.9 (8.3-11.8)	0.064
ESR (mm/h)**	29 (20-45)	17 (8-35)	0.150
CRP (mg/L)**	30.2 (22.2-55)	9.8 ((0.9-32.3)	0.039

*mean ± SD (min-max), ** median (Q1-Q3)
ALC, Absolute lymphocyte count; AMC, Absolute monocyte count; ANC, Absolute neutrophile count; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; MLR, Monocyte-to-lymphocyte ratio; MPV, Mean corpuscular volume; NLR, Neutrophile-to-lymphocyte ratio; NMR, Neutrophile-to-monocyte ratio; PLR, Platelet-to-lymphocyte ratio; PLT, Platelet count; SAT, Serum agglutination test; WBC, White blood cell count.

Discussion

This study indicates that the readily accessible and cost-effective inflammatory markers CRP, WBC, and NMR can serve as indicators of OI in brucellosis. In previous studies, peripheral arthritis was predominantly observed in the pediatric population, whereas sacroiliitis and spondylitis were more frequently identified in adolescents and adults.[8,9] Our study also revealed that patients with OI were older than the others, suggesting the potential utility of these markers, particularly in the adolescent age group. Some studies have indicated that OI in childhood brucellosis is more prevalent among males[9,10], while others have suggested a higher incidence in females.[11,12] In our study, no significant gender difference was observed between patients with and without OI. In the group with OI, the SAT titer was ≥1/640 at diagnosis, and it was statistically different from the group without OI. Although the relationship between SAT titers and disease severity or the presence of complications has not been established, our findings were consistent with those in the study by Çiftdoğan et al. regarding the serologic test results.[13]

Moreover, in the presence of osteoarticular complications, the literature indicates a recommendation for a combined antibiotic treatment regimen lasting 3-6 months to achieve a complete cure and prevent relapse.[14,15] In our study, the treatment duration for patients with osteoarticular disease was significantly longer due to delayed radiological and clinical improvement. It is noteworthy that adolescents may be at risk of experiencing antibiotic side effects due to prolonged treatment.

Kayaaslan and colleagues, in their study involving 700 adult patients, found that CRP and ESR values were significantly elevated in those with hepatitis, epididymoorchitis, neurobrucellosis, and OI.[16] A similar multicenter study in China also demonstrated that increased ESR and CRP levels were associated with complicated brucellosis.[17] Research on pediatric patients with osteoarticular complications supports these findings in adults.[13,18] In our study, CRP levels were significantly higher in the group with OI. However, there was no statistically significant difference between the groups concerning ESR elevation. This discrepancy might be because the study was based on blood test results taken at the time of admission, with CRP rising faster than ESR.[19] For more accurate disease monitoring, serial measurements of ESR might be necessary. Upon admission, evaluating CRP levels in patients presenting with joint pain at admission could provide more accurate information regarding OI.

Several mechanisms may explain the hematological changes seen in brucellosis, such as hypersplenism, bone marrow suppression, direct bacterial infection of hematologic cells, and immune-mediated destruction, which can result in leukopenia, anemia, and thrombocytopenia.[20] Our study found that the mean WBC was lower in patients with OI, although the groups had similar thrombocyte levels. Recent research highlights that LMR, NLR, and PLR are valuable markers of systemic inflammation in various diseases.[21-23] Olt et al. reported a significant decrease in NLR in brucellosis patients compared to healthy individuals and a higher median NLR in those with arthritis.[24] Another study observed significantly elevated PLR and NLR in children with *Brucella* arthritis.[25] In our study, only the NMR, which has been shown to be beneficial in sepsis, COVID-19, and non-infectious inflammation, was significantly higher in patients with OI.[26-28] To the best of our knowledge, this is the first study evaluating NMR in brucellosis. MPV has also been identified as an inflammation marker in many diseases, with two studies indicating higher MPV in children with arthritis-positive brucellosis compared to healthy controls and those with arthritis-negative brucellosis.[21,25,29] Sen et al. found lower MPV in brucellosis patients with specific organ involvement versus those with uncomplicated brucellosis. In our study, mean MPV was lower in the OI

group, but this difference was not statistically significant.[30]

Our study has several limitations. First, since our study is retrospective, we could only evaluate the blood tests taken at the time of the patients' initial presentation. Changes in inflammatory markers during the follow-up could not be observed. Second, the design of the study does not include a control group. Third, due to the retrospective nature of the study, the patients' symptoms and the duration of these symptoms could not be analyzed in detail. Consequently, the relationship between the stage of infection (acute, subacute, or chronic) and inflammatory markers could not be evaluated.

In conclusion, lower WBC and higher CRP and NMR levels can serve as indicators for predicting OI at the time of admission. These readily accessible markers could assist clinicians in the early identification of complications, facilitating timely intervention. Prospective studies with larger cohorts and serial marker evaluations are required to validate and expand on our results, improving the accuracy and reliability of inflammatory markers in diagnosing and managing osteoarticular complications in pediatric brucellosis.

Ethical approval

The study was approved by the Necmettin Erbakan University Ethics Committee (date: 05.07.2024, number: 2024/5064).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: EB; data collection: ŞKTÖ, ZB; analysis and interpretation of results: EB; draft manuscript preparation: EB, ŞKTÖ, ZB. All authors reviewed the results and approved the final version of the manuscript.

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