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Original Article *Özgün Araştırma*

EVALUATION OF PAIN PREVALENCE AND QUALITY OF IN BRUCELLA CASES

Brucella Olgularında Ağrı Prevalansı ve Yaşam Kalitesinin Değerlendirilmesi

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ABSTRACT

Objective: Pain is an inevitable symptom in Brucellosis, which causes a wide clinical spectrum. In this study, we aimed to examine the effect of pain on presence, severity, localization, analgesic intake and quality of life in patients diagnosed with Brucella.

Materail and Methods: Patients diagnosed with Brucella based on clinical and laboratory findings were included in the study. Age, gender, clinical stage of Brucella, organ involvement, serum C-reactive protein (CRP) level and standard tube agglutination test (STA) titer of the patients were recorded. The Brief Pain Inventory (BPI) and the Turkish Version of the World Health Organization Quality of Life Scale Short Form (WHOQOL-BREF-TR) were administered face-to-face to the patients.

Results: The median age of 92 Brucella patients included in the study was 40.5 years. 54.3% of the patients were male and 45.7% were female. At admission, 57.6% were acute, 31.5% subacute, and 10.9% chronic. Organ involvement was present in 31.5% of the patients. At the time of diagnosis, 89.1% of the patients had pain complaints. Pain localization was most frequently in the knee, back, hip and shoulder, respectively. 51.1% of the patients were using nonsteroidal anti-inflammatory drugs (NSAIDs) at least once a day. There was no statistically significant correlation between age, disease stage, organ involvement, serum CRP level and STA titer and WHOQOL-BREF and VAS measurement values. WHOQOL-BREF Psychological (p=0.003) and WHOQOL-BREF Social (p=0.008) measurement values were found to be higher in women than men.

Discussion and Conclusion : Pain is a common symptom in Brucella patients. Regardless of age, laboratory parameters and organ involvement, pain in Brucella patients should be questioned at all clinical stages. It affects the quality of life and may cause undesirable side effects by causing frequent painkiller intake.

Keywords: *Brucellosis, Pain, Organ involvement, Clinical stage, Laboratory parameters*

ÖZ

Amaç: Geniş bir klinik spektruma neden olan Brusellozda ağrı kaçınılmaz bir semptomdur. Bu çalışmada Bruselloz tanılı hastalarda ağrının varlığı, şiddeti, lokalizasyonu, ağrı kesici kullanımı ve yaşam kalitesi üzerine etkisini inceledik.

Gereç ve Yöntemler: Klinik ve laboratuvar bulgularına göre Bruselloz tanısı alan hastalar çalışmaya dahil edildi. Hastaların yaş, cinsiyet, Brusellozun klinik evresi, organ tutulumu, serum C-reaktif protein (CRP) düzeyleri ve standart tüp aglütinasyon testi (STA) titresi kaydedildi. Skorlar, Kısa Ağrı Envanteri (BPI) ve Dünya Sağlık Örgütü Yaşam Kalitesi Ölçeği Kısa Form Türkçe Versiyonu (WHOQOL-BREF-TR) ile hastalarla yüz yüze seanslarda elde edildi.

Bulgular: Çalışmaya dahil edilen 92 Brusella hastasının medyan yaşı 40.5 idi. Hastaların %54.3'ü erkek, %45.7'si kadındı. Başvuru sırasında %57,6'sı akut, %31.5'i subakut ve %10,9'u kronik Bruselloz idi. Hastaların %31.5'inde organ tutulumu mevcuttu. Tanı anında hastaların %89,1'inde ağrı şikayeti vardı. Ağrı lokalizasyonu en sık sırasıyla diz, sırt, kalça ve omuzdaydı. Hastaların %51.1'i günde en az bir kez nonsteroid antiinflamatuar ilaç kullanıyordu. Yaş, hastalık evresi, organ tutulumu, serum CRP düzeyi ve STA titresi ile WHOQOL-BREF ve VAS ölçümü değerleri arasında istatistiksel olarak anlamlı ilişki bulunmadı. WHOQOL-BREF Psikolojik (p=0.003) ve WHOQOL-BREF Sosyal (p=0.008) ölçümü değerleri kadınlarda erkeklere göre daha yüksek bulundu

Sonuç: Ağrı Bruselloz hastalarında sık görülen bir semptomdur. Laboratuvar parametreleri ve organ tutulumu ne olursa olsun Bruselloz hastalarının ağrıları hastalığın tüm evrelerinde değerlendirilmelidir. Ağrı semptomları bu hasta grubunda yaşam kalitesini etkiler ve sık ağrı kesici kullanımına neden olarak istenmeyen yan etkilere neden olabilir.

Anahtar Kelimeler: *Bruselloz, Ağrı, Organ tutulumu, Klinik evre, Laboratuvar parametreleri*

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INTRODUCTION

Brucellosis is the most common zoonosis in the world and is transmitted to humans via animals infected with Brucella bacteria (1). Approximately 500,000 cases of Brucellosis are reported annually, and it constitutes a critical health problem in many countries, especially in Middle East and Southeast Asian countries (2). Turkey is reportedly one of the countries to which Brucellosis is endemic (3). Brucello-sis can be transmitted through the consumption of unpasteurized milk and unpasteurized dairy products, via Brucel-la bacteria contacting damaged skin, or via inhalation from sick animals (4).

Brucella bacteria that are phagocytosed by macrophages and transported to the lymphatic system induce systemic infection by multiplying in the musculoskeletal system, the genitourinary system, the gastrointestinal system, the central nervous system, the cardiovascular system, the respiratory system, and the skin (5). Fever is the most common symptom of Brucellosis, while arthralgia, myalgia, nausea, diarrhea, and abdominal pain are nonspeci-c symptoms. Brucellosis has a wide range of clinical manifestations because it can affect every organ. Although mortality from Brucella infections increases with cardiovascular system involvement in Brucellosis, the mortality rate is 0.8–5% (6).

The diagnosis of Brucellosis is made using serological tests, which measure the amount of IgM/IgG antibodies and bacterial growth in blood or synovial fluid cultures. A stand-ard tube agglutination test (SAT) with a titer of ≥ 1:160 indicates a positive diagnosis of Brucellosis and is the most common diagnostic method employed in endemic regions. The enzyme-linked immunosorbent assay (ELISA) and pol-ymerase chain reaction (PCR) are two other types of diagnostic tests used for B

rucellosis diagnosis (7).

Evaluating the level of pain experienced by a patient is crucial in many diseases because physical, psychological, and social functions are impaired due to the multidimensional nature of pain, and pain may adversely affect the treatment process of the existing disease. To the best of our knowledge, no study has been conducted on pain as a symptom of bBrucellosis. In this study, we examined the effect of pain on presence, severity, localization, painkiller use, and quality of life in patients diagnosed with Brucellosis.

MATERIALS AND METHODS

The study was conducted at the Infectious Diseases Clinic of (BLİNDED) Hospital between October 2021 and January 2022. From patient serum samples sent to the microbiolo-gy laboratory with a preliminary diagnosis of Brucellosis, patients between the ages of 18–65 years who had an SAT titer of 1/160 and above and were diagnosed with Bru-cellosis were selected for inclusion in the study. Patients with cognitive dysfunction who had been treated for any condition, including cancer pain, neuropathic pain, pain due to rheumatic diseases, or pain due to recent surgery or trauma, were excluded from the study. Age, sex, clinical stage of the Brucellosis, organ involvement, serum C-reactive protein (CRP) levels, and the SAT titer of the patients were recorded in specially prepared forms.

The scores were obtained using the Brief Pain Inventory (BPI) and the World Health Organization Quality of Life Scale Short Form Turkish Version (WHOQOL-BREF-TR) in face-to-face sessions with the patients. Questionnaires were administered to each patient only once. When the BPI and WHOQOL-BREF-TR was administered, the stage of the patient's disease (beginning, during and after treatment) was noted simultaneously during the BPI and WHOQOL-BREF-TR.

BPI: this is a short, easy-to-apply assessment method used to assess pain. For pain severity measurements, the answer is captured with a simple numerical evaluation scale of 0 to 10 and it is de-ned as VAS (visual analog scale). Pain localization is determined by marking the area where the patient feels pain on a photograph. The methods or drugs used to provide analgesia, and the frequency of use are also rated in numbers (8).

WHOQOL-BREF-TR: The scale consists of 27 questions that measure general health status and physical, psychological, social, and environmental well-being. Because each domain independently indicates the quality of life in its own -eld, -eld scores are calculated between 4 and 20. The higher the score, the higher the quality of life (9).

Statistical Analysis

The Number Cruncher Statistical System software version 2007 (Kaysville, Utah, USA) was used to run statistical tests. Continuous variables were evaluated for normal distribution using the Saphiro–Wilk test, histograms, and the Q–Q plot, and only WHOQOL-BREF-TR score variables for the psychology and environment -elds were found to have continuous variables with a normal distribution. All continuous variables are presented as median values (-rst–third quartile) to ensure the longitudinal integrity of the study. Categorical variables are presented as frequency and percentage distributions. The Mann–Whitney U test was used to compare continuous variables between two groups, and the Kruskal–Wallis H test was used to compare more than two groups. Because most of the continuous variables did not exhibit a normal distribution, the Spearman correlation coeficient was used to assess the correlation between two continuous variables. P values of 0.05 and above in the 95% con-dence interval were considered statistically signi-cant.

RESULTS

The demographic and clinical characteristics of the 92 patients comprising the study population are summarized in Table 1. The median age of all patients was 40.5 years (28–50 years). Fifty patients (54.3%) were male, and 42 (45.7%) were female. At admission, 53 (57.6%) of the Bru-cellosis cases were acute, 29 (31.5%) were subacute, and 10 (10.9%) were chronic. Organ involvement was present in 29 (31.5%) of the cases. Organ involvement was most common in the -rst two rows, with 13 patients (14.1%) also having spondylitis and discitis, while liver involvement was present in 10 patients (10.9%). Eightytwo (89.1%) of the patients had pain at the time of

diagnosis, -ve (5.4%) did not have pain, and the other -ve patients (5.4%) were unsure if they had pain.

The demographic and clinical characteristics of the 92 patients comprising the study population are summarized in Table 1.

Table 1: Demographic and clinical characteristics of the study population.

Variables		**n (%)**	**Median (1st -3rd quartile)**
Age, year			40.5 (28 – 50)
Sex			
Male		50 (54.3)	
Female		42 (45.7)	
Clinical stage			
Acute		53 (57.6)	
Subacute		29 (31.5)	
Chronic		10 (10.9)	
Organ involvement		29 (31.5)	
Discitis		13 (14.1)	
Spondylitis		13 (14.1)	
Hepatitis		10 (10.9)	
Sacroileitis		6 (6.5)	
Orchitis		4 (4.3)	
CRP			7.68 (3.12 – 17.38)
Brucella tube agglutination			640 (320 – 1280)
Pain at the time of diagnosis	There is	82 (89.1)	
	None	5 (5.4)	
	Not sure	5 (5.4)	
Pain location			
Knee		51 (55.4)	
Waist		37 (40.2)	
Hip		22 (23.9)	
Shoulder		3 (3.3)	
Frequency of taking NSAID			
Not everyday		39 (42.4)	
1-2 per day		47 (51.1)	
3-4 times a day		5 (5.4)	
5-6 a day		1 (1.1)	

Abbreviations: CRP: C-reactive protein, NSAİD: Non-steroidal anti-inflammatory drug.

The median age of all patients was 40.5 years (28–50 years). Fifty patients (54.3%) were male, and 42 (45.7%) were female. At admission, 53 (57.6%) of the Brucello-sis cases were acute, 29 (31.5%) were subacute, and 10 (10.9%) were chronic. Organ involvement was present in 29 (31.5%) of the cases. Organ involvement was most common in the first two rows, with 13 patients (14.1%) also having spondylitis and discitis, while liver involvement was present in 10 patients (10.9%). Eighty-two (89.1%) of the patients had pain at the time of diagnosis, five (5.4%) did not have pain, and the other ve patients (5.4%) were unsure if they had pain. Although the pain was most common in the knees for 51 patients (55.4%), it was localized in the lumbar region for 37 patients (40.2%). When questioned regarding the frequency of nonsteroidal anti-inflammatory drug (NSAID) use, the most common frequency was once or twice daily, reported by 47 patients (51.1%). The second most common frequency was nondaily NSAID use, which was reported by 39 patients (42.4%).

The scores from the WHOQOL-BREF-TR evaluation of all patients are presented in Table 2.

Table 2: WHOQOL-BREF sub-parameters and Visual Analog Scale measurement values of the study population (n=92).

Measurement variables	Median (1st – 3rd quartile)
VAS	5.0 (3.25 – 7.0)
WHOQOL-BREF	
General	6.0 (4.25 – 7.0)
Physically	18.5 (15.0 – 23.0)
Psychological	20.0 (16.0 – 22.0)
Social	10.0 (8.25 – 12.0)
Environment	24.5 (21.0 – 27.0)

Abbreviations: VAS: visual analog scale, WHOQOL-BREF: World Health Organization Quality of Life assessment tool**.**

In the correlation analysis of age, WHOQOL-BREF-TR scores, and visual analog scale (VAS) measurement values, age was evaluated in terms of three WHOQOL-BREF-TR sub-parameters: general ($r=-0.251$, $p=0.016$), social ($r=-0.222$, $p=0.033$), and environment ($r=-0.212$, $p=0.042$), as there was no statistically significant correlation with the other sub-parameters and the VAS meas-urements.

The results of a comparison of the WHOQOL-BREF-TR sub-parameters and the VAS measurement values of the two sexes are summarized in Table 3.

Table 3: Comparison of WHOQOL-BREF and Visual Analog Scale measurement values between genders.

Variables	Male (n=50) Median (1st – 3rd quartile)	Female (n=42) Median (1st – 3rd quartile)	p value[α]
WHOQOL-BREF			
General	6 (4 – 8)	5 (4.75 – 6)	0.103
Physically	21 (16 – 24.25)	17 (14 – 22)	0.065
Psychological	21 (18 – 23.25)	18 (14.75 – 21)	**0.003**
Social	11 (9 – 12)	9 (7 – 11)	**0.008**
Environment	25 (21 – 27)	23 (20 – 27)	0.119
VAS	5.0 (3.75 – 7.0)	5.0 (3.0 – 7.25)	0.840

Abbreviations: VAS: visual analog scale, WHOQOL-BREF: World Health Organization Quality of Life assessment tool.[α]Mann-Whitney U test.

From the comparison, the WHOQOL-BREF-TR psychological (p=0.003) and WHOQOL-BREF-TR social (p=0.008) median measurement values were found to be higher for males.

Evaluation of the WHOQOL-BREF-TR sub-parameters and the VAS measurements between clinical stages did not yield any statistically signi-cant differences (Table 4).

Table 4: Comparison of WHOQOL-BREF and Visual Analog Scale measurement values between Clinical Stages.

Variables	Acute (n=53) Median (1st – 3rd quartile)	Subacute (n=29) Median (1st – 3rd quartile)	Chronic (n=10) Median (1st – 3rd quartile)	p value[β]
WHOQOL-BREF				
General	6 (5 – 7)	6 (4 – 7)	5 (2.75 – 6.25)	0.293
Physically	18 (13.5 – 22)	21 (16.5 – 24)	19.5 (14 – 28.25)	0.061
Psychological	19 (16 – 22)	21 (16.5 – 23)	19 (17 – 21)	0.713
Social	10 (9 – 12)	10 (7 – 12)	8 (8 – 10.5)	0.111
Environment	24 (21 – 27)	25 (21 – 27)	24.5 (20 – 27.25)	0.971
VAS	5 (4 – 7.5)	5 (2 – 7)	6 (3 – 7)	0.400

Abbreviations: VAS: visual analog scale , WHOQOL-BREF: World Health Organization Quality of Life assessment tool. [β]Kruskal Wallis test.

A directly proportional and statistically signi-cant correlation was found between serum CRP levels and SAT titer (r=0.408, p<0.01). However, no statistically signi-cant correlation was found between the Brucella tube agglutination measurement values and the WHOQOL-BREF-TR sub-parameters and VAS measurement values. Furthermore, with the exception of the serum CRP levels and the WHOQOL-BREF-TR general sub-parameter (r=−0.205, p=0.050), no signi-cant correlation was found between the WHOQOL-BREF-TR sub-parameters and the serum CRP levels (Table 5)

Table 5. Correlation assessment between Brucella tube agglutination and CRP measurement values, and WHO-QOL-BREF sub-parameters and Visual Analogue Scale in the study population.

		WHOQOL-BREF					
Variables		**General**	**Physically**	**Psychological**	**Social**	**Environment**	**VAS**
Brucella tube agglutination	**r**	-0.082	-0.081	0.090	0.100	0.077	0.142
	p value	0.440	0.445	0.393	0.345	0.467	0.178
CRP value	**r**	-0.205	-0.112	0.017	-0.051	-0.073	0.185
	p value	**0.050**	0.289	0.870	0.629	0.490	0.077

Abbreviations: VAS: visual analog scale. Note that r indicates Spearman's correlation coefficient.

No statistically signi-cant difference was found via a comparison of the WHOQOL-BREF-TR sub-parameters and the VAS measurement values of patients with and without organ involvement (Table 6).

Table 6: Comparison of WHOQOL-BREF sub-parameters and Visual Pain Scale measurement values in patients with and without organ involvement.

	Organ involvement		
Variables	**Yes (n=29) Median (1st – 3rd quartile)**	**No (n=63) Median (1st – 3rd quartile)**	**p value$^{\alpha}$**
WHOQOL-BREF			
General	5 (4 – 7)	6 (5 – 7)	0.479
Physically	19 (13 – 24)	18 (16 – 23)	0.711
Psychological	20 (17 – 22.5)	20 (16 – 22)	0.727
Social	10 (9 – 12)	10 (8 – 12)	0.405
Environment	24 (22 – 27)	25 (21 – 27)	0.946
VAS	6 (4.5 – 7.5)	5 (3 – 7)	0.062

Abbreviations: VAS: visual analog scale , WHOQOL-BREF: World Health Organization Quality of Life assessment tool. $^{\alpha}$Mann-Whitney U test.

DISCUSSION

Some occupational groups, including farmers, shepherds, veterinarians, dairy industry personnel, slaughterhouse personnel, microbiology laboratory personnel, and people living in endemic areas, are at risk of Brucella infection. Although Brucellosis has been observed in people of all ages, it has been established that Brucellosis is more common in economically active young adults who get infected due to occupational exposure (10). Occupational groups of patients diagnosed with Brucellosis were not evaluated in this study, but their median age was 40.5, which is the young active adult age period.

There is the question of whether sex is a risk factor for Brucella infection. Although the cause could not be clearly identi-ed when investigated, it has been reported that the incidence of

Brucella infection is higher in males, as was the case in our study (11). However, there are also studies reporting that Brucellosis is observed equally in both sex-es (12). The remarkable observation in our study was that the WHOQOL-BREF-TR psychological and WHOQOL-BREF-TR social median values were lower for female Brucellosis patients than for males. According to some researchers, however, severe forms of the disease are more common in women (13). However, in our study, we did not -nd any differences between men and women for the other WHO-QOL-BREF-TR sub-parameters and the GEE measurements.

Brucella infection is classi-ed as acute (0–2 months), subacute (2–12 months), or chronic (12 months and over) based on the duration of the symptoms and clinical manifestations (14). A study reported that complications were more common in subacute and chronic Brucellosis than in acute Brucellosis (15). However, this may be related to a delayed Brucellosis diagnosis and prolonged exposure to Brucella bacteria. In our study, 57.6% of the cases were acute, 31.5% were subacute, and 10.9% were chronic. There was no difference between patients at different clinical stages in terms of pain and quality of life. Inflammatory markers, such as serum CRP levels, erythrocyte sedimentation rate, serum lactate dehydrogenase levels, and alkaline phosphatase levels, may be high in individuals with Brucella infections, and liver involvement causes high liver transaminase levels (16). In a study investigating the relationship between acute to subacute Brucellosis or chronic Brucellosis and high values for certain laboratory parameters (SAT titer, growth in culture), it was reported that a titer of 1/320 and above is more common in acute to subacute cases than in chronic cases (17). Regarding the laboratory parameters examined in our study, the median CRP was 7.68 mg/dl and the SAT titer was 1/640 and above. However, no signi-cant correlation was found between these laboratory parameters and the WHOQOL-BREF-TR sub-parameters and VAS measurement values. Based on this result, we propose that the pain and quality of life of Brucellosis patients should be evaluated independently of laboratory values.

In Brucella infections, the musculoskeletal, gastrointestinal, hematologic, genitourinary, neural, respiratory, and cardiovascular systems are the most frequently aected organ systems (14). With gastrointestinal involvement, hepatic abscess, granuloma, and peritonitis are observed, while cough, dyspnea, and pleurisy accompany lung involvement, and meningitis, encephalitis, myelitis, and brain abscess develop with neural involvement (18). Although death from Brucellosis is rare, the most common cause of death is cardiovascular system involvement (19). In our study, 31.5% of the patients had organ involvement. The most common clinical manifestations were spondylitis, discitis, liver involvement, sacroiliitis, and orchitis.

Involvement of the musculoskeletal system, which can occur in all stages of the disease (subacute, acute, and chron-ic), has been reported as the most frequently involved system in many studies (20,21). Of the clinical forms of the disease (i.e., peripheral arthritis, sacroiliitis, and spondyli-tis), peripheral arthritis is the most common, affecting the knees, hips, and ankles and causing pain, swelling, increase in local temperature, and limited movement in the joint (22). Spondylitis, the most severe form of osteoarticular involvement, often causes residual bone damage despite treatment. It often a-ects the lumbar and thoracic vertebrae and causes back pain and low back pain (23). Radiological imaging methods are used to detect osteoarticular complications; however, osteoarticular changes are a radiological-ly late occurrence (24). Therefore, it is important to assess the pain experienced by Brucellosis patients to detect organ involvement in the early stages of the disease.

In symptomatology studies on Brucella infections, low back pain, headaches, joint pain, and muscle pain are the main complaints reported (25). In our study, 89.1% of the patients had pain complaints at the time of diagnosis. The localization of the pain experienced during the preceding week was most frequently in the knees, waist, hips, and shoulders. The median VAS value—an evaluation of pain intensity for the preceding week—was 5, and 51.1% of the patients were using NSAIDs once or twice a day. In a study including 202 Brucellosis patients whose osteoarticular system complications were diagnosed via physical examination and radiological findings obtained using diagnostic imaging tools, the authors reported that the disease should be considered in di-erential diagnoses in countries such as Turkey, where Brucellosis is endemic—especially for patients with low back and sacroiliac joint pain (26).

Although this study is a single-center study, the number of participants in our study is relatively high because it was conducted in an endemic region. Because the hospital at which this study was conducted is the largest in Eastern Anatolia, we were able to evaluate patients with di-erent stages of Brucellosis (subacute, acute, and chronic). However, the inclusion of radiological data on patients with pain symptoms, children, and the elderly is a limitation of our study.

According to the results of this study; that Brucella patients need pain treatment almost every day; we saw that they relieved the pain with simple analgesics that they used on their own or with the recommendation of their family phy-sicians. Patients often see their pain as a natural course of the disease and often do not convey this to the infectious diseases specialist who undertakes their treatment. These patients should be evaluated together with an algology specialist in order to prevent excessive painkiller intake and to provide an effective treatment in pain management.

In conclusion, pain is a common symptom in Brucellosis patients. Regardless of laboratory parameters and organ involvement, the pain of Brucellosis patients should be assessed at all stages of the disease. Pain symptoms a-ect the quality of life in this patient group and may cause undesirable side e-ects by inducing frequent painkiller use.

Ethics Committee Approval: Health Sciences University Van Training and Research Hospital Ethics Committe of Clinical Research , date: 11/09/2021 with issue number: 11/09/2021 - 06.

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