Turkish Journal of Geriatrics
DOI: 10.31086/tjgeri.2018344049
2018;21(3):346-353

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Received: 07/04/2018
Accepted: 21/07/2018

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RESEARCH

BRUCELLOSIS IN GERIATRIC PATIENTS: IS THE DISEASE COURSE MORE SERIOUS?

Abstract

Introduction: Resistance to infectious diseases is impaired in the geriatric population. Delayed diagnosis and poor prognosis are common problems in this population because complaints are often considered natural consequences of old age. Thus, we evaluated the clinical and laboratory features of brucellosis in geriatric patients that we treated and followed up. We did not find any similar studies in the literature.

Materials and Method: Patients aged ≥65 years who were diagnosed with brucellosis and hospitalised between January 2012 and October 2017 were retrospectively evaluated for demographic characteristics and clinical, epidemiological and laboratory parameters.

Results: The study included 71 geriatric patients [29 male (40.8%) and 42 female (59.2%)]. The mean age was 70.64±6.5 years. Twenty-four patients had acute, thirty had sub-acute and nine had chronic brucellosis, whereas eight had relapsed disease. Most common symptoms were fatigue and back pain. Most common clinical signs were organomegaly and fever. Wright and Coombs test results and blood cultures were positive in 76%, 22.5%, and 19.7% of patients, respectively. Focal involvement was detected in 36 (50.7%) patients. The most commonly preferred treatment combination was rifampicin/doxycycline.

Conclusion: Brucellosis can present with non-specific clinical signs in the geriatric population compared with those in the general population. This difference should be considered when treating geriatric patients, particularly in areas endemic for brucellosis.

Keywords: Geriatrics; Brucellosis; Complications; Prognosis

ARAŞTIRMA

GERİATRİK HASTALARDA BRUSELLOZ: DAHA CİDDİ Mİ SEYREDER?

Öz

Giriş: Geriatrik popülasyonda enfeksiyon hastalıklarına karşı direnç azalmaktadır. Gecikmiş tanı ve kötü prognoz şikayetlerin genellikle yaşlılığın doğal sonuçları olarak kabul edildiğinden bu popülasyonda sık görülen sorunlardır. Bu nedenle tedavi ve takibi yapılan geriatri yaş grubundaki hastalarında brusellozun klinik ve laboratuvar özellikleri değerlendirildi. Literatürde benzer herhangi bir çalışmaya rastlanmadı.

Gereç ve Yöntem: Ocak 2012 ve Ekim 2017 tarihleri arasında, bruselloz tanısı konan ve hastaneye yatırılan 65 yaş üstü hastalar demografik özellikleri, klinik, epidemiyolojik ve laboratuar parametreleri açısından retrospektif olarak değerlendirildi.

Bulgular: Çalışmaya 71 geriatrik hasta dahil edildi [29 erkek (%40.8) ve 42 kadın (%59.2)]. Yaş ortalaması 70.64±6.5 idi. Yirmi dört hasta akut, otuz hasta subakut ve dokuz hasta kronik bruselloz, sekiz hasta ise relapstı. En sık görülen semptomlar yorgunluk ve sırt ağrısıydı. En sık görülen klinik belirtiler organomegali ve ateşti. Wright ve Coombs test sonuçları ve kan kültürleri sırasıyla hastaların %76'sında, %22.5'inde ve %19.7'sinde pozitif idi. Fokal tutulum 36 (%50.7) hastada saptandı. En çok tercih edilen tedavi kombinasyonu, rifampisin/doksisiklin idi.

Sonuç: Bruselloz genel populasyondakilere göre geriatrik popülasyonda spesifik olmayan klinik bulgularla ortaya çıkabilir. Bu fark, özellikle bruselloz için endemik olan bölgelerde geriatrik hastaları tedavi ederken dikkate alınmalıdır.

Anahtar sözcükler: Geriatri; Bruselloz; Komplikasyonlar; Prognoz

INTRODUCTION

Brucellosis is endemic in Turkey, with most cases occurring in the central, eastern and southeastern Anatolian provinces. Although the number of patients has gradually decreased, the disease currently is not exactly under control (1). Brucellosis is the most common zoonosis worldwide; this systemic disease can be transmitted by contact with body fluids, urine and placenta of infected animals and/or ingestion of raw milk, dairy products and meat of these animals (2).

Brucellosis manifests in a wide range of cases from asymptomatic ones to those with serious disease (3). The disease is classified according to the duration of symptoms as acute (<8 weeks), sub-acute (8-52 weeks) or chronic (>1 year). In case of organ involvement, the disease is said to have focal involvement or complication (4). Relapse is described as the recurrence of brucellosis signs and symptoms within 1 year after completion of treatment course, elevated IgG antibody titres, newly emerging pathological and radiographical findings or growth detection in recent body samples (4,5). Although the disease can occur in all age groups, young adults and middle-aged individuals are most commonly affected. Its incidence in children and the elderly is relatively low (5). Old age (≥65 years) is primarily characterised by reduced biological capacity reserves (6). Infectious diseases present with atypical clinical course in elderly patients due to the impact of environmental factors in addition to their genetic constitution and acquired chronic changes (7). Delayed diagnosis and poor prognosis are common problems in this patient group because complaints are often considered a natural consequence of old age (8). Careful evaluation of clinical symptoms and signs in the elderly is the best approach for brucellosis. Therefore, we aimed to evaluate the clinical and laboratory features of brucellosis in geriatric patients and to compare the clinical course of the disease in this population in previous studies. We did not find any similar studies reported in the literature.

MATERIALS AND METHOD

We performed a retrospective analysis of 71 patients with brucellosis aged ≥65 years who were admitted to the Firat University Medical School Hospital Department of Infectious Diseases between 1 January 2012 and 10 January 2017. Brucellosis was diagnosed based on the growth of *Brucella* in blood cultures or positive titres on Wright and/or Coombs tests in cases without culture growth. Clinical, epidemiological and laboratory variables at diagnosis and before treatment onset and demographic characteristics were obtained. The study was approved by the Firat University Ethics Committee for Non-interventional Studies on 22 March 2018.

The data were analysed using the SPSS version 22 software. Visual and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk's test) were used to evaluate the normality of distributions. Normally distributed variables were expressed as the mean±standard deviation and non-normally distributed variables as the median (minimum–maximum). Categorical variables were presented as frequency and percentage values. Continuous variables were compared using either the Mann–Whitney *U* test or Student's *t*-test based on the normality of data distribution. Multiple comparisons were performed using the one-way ANOVA or Kruskal–Wallis tests. Categorical variables were compared using the Pearson's χ^2 and Fisher's exact tests. The level of statistical significance was $p<0.05$.

RESULTS

Demographic results

Among the 71 patients with brucellosis [29 (40.8%) male, 42 (59.2%) female; overall mean age, 70.64±6.5 years (range, 65–92 years); median age, 68 years], 24 (33.8%) had acute, 30 (42.3%) had sub-acute and nine (12.7%) had chronic brucellosis, whereas eight (11.3%) had relapsed disease. Among patients with sub-acute disease, the rate of osteoarticular complications was 50%, which was significantly higher than

that in patients with acute disease ($p<0.05$). Specific risk factors were found in 20 (28.1%) patients with brucellosis; 13 patients (65%) had a history of stock farming, 15 (75%) had ingested raw milk and fresh cheese, four (20%) had a family history of brucellosis and 55 (77.4%) lived in the rural area.

Symptoms and physical examination findings

The most common symptoms were fatigue (87.3%), back pain (59.1%), fever (52.1%), night sweats (52.1%) and myalgia (47.8%). The most common clinical signs were organomegaly (28.1%) and fever (25.3%; Table 1).

Table 1. Symptoms and clinical signs.

Symptom/sign	n(%)
Fatigue	62(87.3%)
Back pain	42(59.1%)
Fever	37(52.1%)
Night sweats	37(52.1%)
Myalgia	34(47.8%)
Arthralgia	14(19.7%)
Weight loss	7(9.8%)
Headache	6(8.1%)
Neck pain	5(7.1%)
Nausea-vomiting	5(7.1%)
Scrotal pain	1(1.4%)
Skin rash	1(1.4%)
Signs	
Organomegaly	20(28.1%)
Hepatomegaly	9(12.6%)
Splenomegaly	5(7.0%)
Hepatosplenomegaly	6(8.4%)
Fever	18(25.3%)
Cardiac murmur	6(8.4%)
Meningeal irritation	3(4.2%)
Skin rash	1(1.4%)
Swelling of scrotum	1(1.4%)

Laboratory results

C-reactive protein (CRP) levels were high in 55 (77.5%) patients (mean, 32.5±43.8; median, 13; range, 3–286). Erythrocyte sedimentation rate (ESR) was high in 51 (71.8%) patients (mean, 39.4±22.9 median, 34; range, 5–100).

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were elevated above reference values in 19 (26.8%; median, 26; range, 9–241) and 23 (32.4%; median, 41; range, 11–189) patients, respectively.

Median CRP values were 40 (range, 3.1–286) and 12.4 (range, 3–182) in patients with positive and negative blood cultures, respectively ($p<0.05$). No significant relationship was found between other variables ($p>0.05$). Laboratory results are presented in Table 2.

Microbiological results

Of the 71 patients, 54 (76%) had positive standard tube agglutination (STA) test results, 16 (22.5%) had negative STA and positive Coombs test results and one had negative STA and negative Coombs test results but positive *B. melitensis* blood culture results. Overall, *Brucella* species were isolated in blood cultures of 14 (19.7%) patients, 78.6% of whom presented with complications. The complication rate was 43.9% in patients with negative blood cultures ($p<0.05$). No significant difference was found for other variables ($p>0.05$).

Complications

Focal involvement was present in 50.7% of the patients. The most common complication was osteoarticular involvement (69.4%), most often with spondylodiscitis (52.7%; Table 3).

Treatment

The preferred treatment combination was rifampicin/doxycycline in 69% of the patients, followed by rifampicin/doxycycline/aminoglycoside (amikacin/streptomycin) in 26.7%. Additionally, combination treatments, including tetracycline, ciprofloxacin, trimethoprim/sulfamethoxazole and ceftriaxone were also prescribed based on side effects caused by current drugs or presence of local infection. The mean duration of treatment for patients was 134 (38-369). days. Adverse antibacterial drug reactions were observed in 51 (71.8%) patients, with nausea and vomiting being the most common (76.4%), followed by hepatotoxicity (33.3%), nephrotoxicity (23%) and balance disorder and dizziness (11.7%). Treatment was changed in 12 (16.9%) patients due to adverse effects. No patients died of brucellosis during the treatment or follow-up.

Table 2. Laboratory results.

Result	n(%)
Anaemia (male-Hb<14mg/dL and female Hb<12mg/dL)	12 (16.9%)
Thrombocytopenia (platelet count<150,000/mm^3)	8 (11.3%)
Leukopenia (WBC count<4000/mm^3)	4 (5.6%)
Leukocytosis (WBC count>10,000/mm^3)	4 (5.6%)
Lymphocytosis (>45%)	6 (8.5%)
Pancytopenia	1 (1.4%)
Bicytopenia	2 (2.8%)
ALT (>40IU/L)*	19 (26.8%)
AST (>40IU/L)*	23 (32.4%)
ESR (>20mm/h)*	51 (71.8%)
CRP (>5mg/L)*	55 (77.5%)

*ALT: alanine aminotransferase, *AST: aspartate aminotransferase, *ESR: erythrocyte sedimentation rate, *CRP: C-reactive protein

Table 3. Distribution of complications.

Complication	n (%)
Osteoarticular complications	25(69.4%)
Spondylodiscitis	19(52.7%)
Paravertebral abscess	8(22.2%)
Sacroileitis	5(13.8%)
Osteitis	2(5.5%)
Neurobrucellosis	3(8.3%)
Hepatitis	2(5.5%)
Epididymo-orchitis	1(2.7%)
Endocarditis	1(2.7%)
Haematological complications	3(8.3%)
Skin involvement	1(2.7%)
Focal involvement	36(50.7%)

DISCUSSION

The proportion of geriatric population has been increasing worldwide, including Turkey, due to improved standard of living (9). As a result of immune dysfunction caused by ageing, resistance to infections is decreased (10). These adverse outcomes in the elderly can mask signs and symptoms of diseases, leading to delayed diagnosis and treatment. Delayed diagnosis and treatment in brucellosis affects all body systems, and patients present with various symptoms. As a consequence, serious complications which cause morbidity and mortality can occur (5).

Previous studies have compared epidemiological, clinical and laboratory findings and treatment outcomes in children and adults with brucellosis. However, such studies involving geriatric patients were not found in the literature. Therefore, we evaluated the course of brucellosis in geriatric subjects.

Although the incidence of brucellosis in children and the elderly is low (5), it can affect individuals of any age and sex (11). In a study evaluating 1028 patients aged 3–81 years (mean age, 33.7±16.34 years), the disease incidence was commonly observed in patients aged 13–24 years (29%), while those aged ≥67 years accounted for only 2% of the study population (12). The mean age of our patients was 70.64±6.5 years, with more female (59.2%) than male (40.8%) patients, which was similar to that in some other studies (12,13).

In endemic countries, brucellosis is mainly transmitted by the ingestion of unpasteurised milk products, whereas in developed countries, the transmission usually occurs as a result of occupational exposure (14). In a study conducted in Turkey, exposure history included ingestion of unpasteurised fresh cheese and raw milk in 79% of patients, agriculture and stock raising in 35%, and family history of brucellosis in 16% (15). In our study, the most

common routes of transmission were ingestion of raw milk and fresh cheese (75%) and stock raising (65%). Family history of brucellosis was identified in 20% of our patients. In the study by Roushan et al. (16), 73.8% of patients lived in rural areas compared with 77.4% in our study.

Brucellosis can present in different clinical forms (17). Buzgan et al. (12) reported acute, sub-acute and chronic brucellosis rates of 61.6%, 21.6% and 13.6%, respectively; another study reported these rates as 77%, 12.5% and 10.5%, respectively (18). In our study, these rates were found to be 33.8%, 42.3% and 12.7%, respectively. The prevalence of sub-acute brucellosis was considerably higher in our study than in other studies. These results can be explained by the fact that brucellosis symptoms are misjudged as consequences of ageing. Our patients did not get a different diagnosis before brucellosis.

Increased body temperature, which is the most common symptom of brucellosis, was reported in 72.2%–90.5% of patients in many studies (19,20). In our study, 52.1% of high fever was detected. These results indicated that typical brucellosis symptoms may not be very common in the elderly and that patients may present with a non-specific clinical manifestation.

Brucellosis can present with various signs and symptoms because it affects many organs and systems. Many studies have reported fever and organomegaly as the most common symptoms (19,20). Gonen et al. (21) found fever in 60.6%, hepatomegaly in 16.4% and splenomegaly in 15.9% of cases. In our geriatric patients, hepatomegaly, splenomegaly, hepatosplenomegaly and fever were found in 12.6%, 7.0%, 8.4% and 28.1% of patients, respectively. Our data indicated that fever, which is a typical symptom of brucellosis, was detected less frequently in the geriatric population compared with other studies.

Similar to previous studies, our most common laboratory findings were moderate anaemia, leucopoenia, thrombocytopenia and increased liver enzymes, ESR and CRP levels (4,17). Haematological and biochemical tests are of poor diagnostic value in brucellosis (22). While increased CRP levels was the most prominent laboratory finding in acute and sub-acute cases in many studies (4,17), no significant association between CRP levels and different clinical forms of brucellosis was found in our study population ($p>0.05$). However, a positive correlation was observed between increased CRP levels and positive blood culture results ($p<0.05$). This result indicated the importance of performing blood cultures in patients with increased CRP levels.

Isolation of the pathogen from blood cultures varies between 15% and 90% of brucellosis cases (4,17). Isolation from cultures can be achieved in 40%–90% of acute brucellosis cases, although this rate decreases to 5%–20% in chronic brucellosis, focal infection, or complicated cases (23). In our study, the causative pathogen was isolated from blood cultures of 19.7% of the cases, while no significance difference was found in the bacterial growth in blood cultures from different disease stages. Additionally, complications were present in 78.6% and 43.9% of patients with positive and negative blood cultures, respectively ($p<0.05$). The current data suggested that the rate of complications was higher in patients with positive blood cultures than in those with negative blood cultures for *Brucella*. Serological tests are an alternative method for the diagnosis of brucellosis when bacterial isolation is not possible (4,17). In several studies, STA was detected in 87%-95% of cases (4,12,17). Coombs STA test is an alternative for diagnosing brucellosis when STA results are negative. Previous studies have reported 4.8% of patients with positive Coombs STA results and 1.1% with negative results (12). In our study, the proportion of STA-positive patients (76%) was below the estimated rates and that of Coombs STA-positive patients (22.5%) was considerably above the estimated rates; the proportion of seronegative patients was 1.4%. Our results suggested that Coombs STA test should be used in routine practice for di-

agnostic purposes, particularly for geriatric patients with brucellosis with a sub-clinical disease course.

The rate of complications was 20%–40% in several studies (3,12). The complication rate of 50.7% in our study was higher than those in other studies (4,12,17). This result may be explained by delayed diagnosis and treatment in geriatric patients who do not present with typical clinical manifestations for brucellosis. Similar to other studies, the most common complication in our study group was osteoarticular involvement (69.4%), with spondylodiscitis most commonly observed (4,12,17). Osteoarticular complications were present in 50% of patients diagnosed with sub-acute brucellosis, and this rate was significantly higher than that reported for patients with acute brucellosis ($p<0.05$). Kazak et al. (24) reported similar results.

The World Health Organisation has recommended a combination treatment with doxycycline/rifampicin or streptomycin/doxycycline for brucellosis (4). In our study, the most commonly used combination treatment was doxycycline/rifampicin; rifampicin/doxycycline/aminoglycoside combination was particularly preferred in patients with osteoarticular involvement. Hashemi et al. (25) found adverse reactions in 16.8% of patients. In our study, adverse antibacterial drug reactions were observed in 71.8% of patients, and treatment was changed in 16.9% of these patients. Combination treatments including tetracycline, ciprofloxacin, trimethoprim/sulfamethoxazole and ceftriaxone were also prescribed based on the side effects caused by current drugs or presence of local infections. The objectives of brucellosis treatment include prevention of complications and relapse. In a previous study, the relapse rate was reported as 6.4% (21), whereas it was high at 11.3% in our study. These data underlined the importance of post-treatment follow-up for geriatric patients with brucellosis to prevent relapse.

In conclusion, signs and symptoms of brucellosis can present differently than expected in geriatric patients. Atypical clinical presentation can delay diagnosis and treatment, causing serious clinical disease progression with increased complications. These findings indicate that a more comprehensive and prudent investigation course for brucellosis should be followed in geriatric patients. Taken together, we believe that our study would contribute to optimal assessment of geriatric patients with brucellosis.

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