

1-1-2011

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Recommended Citation

BULUT, CEMAL; YETKİN, MELTEM ARZU; YILMAZ, GÜLRUHSAR; ERDİNÇ, FATMA ŞEBNEM; HATİPOĞLU, ÇİĞDEM ATAMAN; KINIKLI, SAMİ; ORAL, BEHİÇ; TÜLEK, NECLA; and DEMİRÖZ, ALİ PEKCAN (2011) "Assessment of the findings on the existence of complications in brucellosis," *Turkish Journal of Medical Sciences*: Vol. 41: No. 2, Article 13. <https://doi.org/10.3906/sag-0908-17>
Available at: <https://journals.tubitak.gov.tr/medical/vol41/iss2/13>

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Assessment of the findings on the existence of complications in brucellosis

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Aim: Brucellosis is a prevalent disease in Turkey. The object of this study was to assess the findings in brucellosis cases with and without complications.

Materials and methods: A total of 324 patients diagnosed with brucellosis between 1999 and 2005 were reviewed retrospectively. The diagnosis of brucellosis was established serologically and/or by positive blood culture. Epidemiologic features, clinical symptoms, and laboratory findings of the patients were assessed in both complicated and noncomplicated brucellosis cases by univariate and multivariate analysis.

Results: The mean age of patients was 44.0 ± 18.3 years (range 15-83 years). In addition, 56% of the patients were male. Animal husbandry (62.7%) and consumption of raw milk and/or fresh cheese (27.7%) were identified as being the main risk factors for brucellosis. Fever, malaise, sweating, and arthralgia were the most frequent clinical symptoms. The most common physical findings were fever, hepatomegaly, and splenomegaly. Complications were detected in 142 of 324 cases (43.8%). Osteoarticular involvement (25.9%) was the most common complication. Dealing with animal husbandry, living in a rural area, being between 31 years and 50 years of age, and an elevated C-reactive protein (CRP) level were significantly associated with the existence of complications by univariate analysis ($P < 0.05$). Elevated CRP level remained independently associated with complications by multivariate analysis ($P < 0.05$).

Conclusion: Elevated CRP levels, in accordance with clinical manifestations of the patient, may be a sign of complications, and needs further investigation.

Key words: Brucellosis, epidemiology, diagnosis, complication

Bruselloz hastalarında komplikasyonların varlığının belirlenmesinde bulguların değerlendirilmesi

Amaç: Bruselloz ülkemizde yaygın olarak görülen bir hastalıktır. Bu çalışmada komplikasyonla seyreden ve seyretmeyen bruselloz olgularında klinik ve laboratuvar bulgularının değerlendirilmesi amaçlandı.

Yöntem ve gereç: Bu çalışmada 1999 ile 2005 yılları arasında bruselloz tanısıyla kliniğimizde takip edilen hastalar retrospektif olarak değerlendirildi. Bruselloz tanısı serolojik olarak veya kan kültüründe etkenin izolasyonu ile konuldu. Komplikasyon gelişen ve gelişmeyen hastaların epidemiyolojik, klinik ve laboratuvar özellikleri tek değişkenli ve çok değişkenli yöntemlerle analiz edildi.

Bulgular: Hastaların yaş ortalamaları $44,0 \pm 18,3$ yıl idi (yaş aralığı 15-83 yıl). Hastaların % 56'sı erkekti. Brusellozun bulaş yolu olarak hastaların % 67,2'sinde hayvancılık, % 27,7'sinde taze süt ve/veya peynir tüketimi idi. Ateş, kırgınlık terleme ve artralji en sık görülen semptomlardı. Ateş, hepatomegali ve splenomegali ise en sık saptanan fizik muayene bulguları idi. Hastaların 142'sinde (% 43,8) komplikasyon saptandı. Osteoartiküler tutulum (% 25,9) en sık saptanan komplikasyon idi. Tek değişkenli analizlerde hayvancılıkla uğraşma, kırsal bölgede yaşama, yaşın 31 ile 50 arasında olması ve yüksek

Received: 05.08.2009 – Accepted: 25.03.2010

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* We have no commercial or proprietary interest in any drug, device or equipment mentioned in the article.

C-reaktif protein (CRP) seviyesi komplikasyon gelişimi ile ilişkili bulundu ($P < 0,05$). Çok değişkenli analizde ise sadece yüksek CRP seviyesi komplikasyon varlığı ile ilişkili bulundu ($P < 0,05$).

Sonuç: Yüksek CRP seviyesi hastaların klinik bulguları ile birlikte değerlendirildiğinde bir komplikasyonun varlığının göstergesi olabilir ve bu hastalarda ileri araştırmalar gerekebilir.

Anahtar sözcükler: Bruselloz, epidemiyoloji, tanı, komplikasyon

Introduction

Brucellosis is still endemic in Mediterranean countries, in Africa, in the Middle East, and Central Asia (1). In Turkey, human brucellosis is particularly an endemic disease. According to the database of the Turkish Ministry of Health, 15,000 cases annually (incidence 22/100,000) of human brucellosis have been reported (2).

Brucellosis is a systemic infection in which any organ or system of the body can be involved. The disease is characterized by non-specific symptoms. Protean clinical manifestations cause difficulty in diagnosis. Late diagnosis can lead to serious complications and significant morbidity. The musculoskeletal system, hepatobiliary system, and nervous system are frequently affected (3).

The object of this study was to assess the findings of brucellosis cases with and without complications.

Materials and methods

This retrospective study was conducted at the Department of Infectious Diseases and Clinical Microbiology of The Health Ministry Ankara Training and Research Hospital between January 1999 and June 2005. Patients over 15 years of age, diagnosed and treated for brucellosis, were enrolled in the study. All patients were evaluated for the systemic involvements of brucellosis. Demographic characteristics, presence, duration of clinical symptoms at admission, history of ingestion of raw milk or milk products, pertinent physical examination findings, and laboratory test results were recorded. Our hospital is one of the major state hospitals in the city, serving not only the 4,500,000 inhabitants of Ankara, but also it is the referral hospital for 11 cities in Central Anatolia.

Diagnosis of brucellosis: Diagnosis was established by one of the following criteria: (1) isolation of *Brucella* spp. from blood samples, (2) a clinical and epidemiological presentation consistent with brucellosis in the presence of a standard tube agglutination test (STA) equal to or higher than 1:160, or (3) a 4-fold increase in titers of STA within 4 weeks.

A seroagglutination test was carried out in all patients. All the blood samples were cultured in BACTEC 9050 system and incubated for at least 21 days. A complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), liver, and renal function tests were also performed. The accepted normal range of the ALT, AST, and CRP were 0-35 U/L, 0-34 U/L, and 0-0.8 mg/dL, respectively. The normal upper limit for ESR was accepted as 20 mm/h for males, and 15 mm/h for females. A hemoglobin level lower than 12 g/L was defined as anemia, and a platelet level lower than 150,000/ μ L was defined as thrombocytopenia. Patients with brucellosis were classified as acute (< 8 weeks), sub-acute (8-52 weeks), and chronic (> 52 weeks) according to the duration of clinical symptoms (4).

Definition of complications: Sacroiliitis, spondylitis, and peripheral arthritis were diagnosed by radiographic abnormalities, detected by one of the following: X-ray, computed tomography, magnetic resonance imaging, or bone scan. Neurobrucellosis includes meningitis, encephalitis, myelitis-radiculoneuritis, brain abscess, epidural abscess, and meningovascular syndromes. Meningitis was diagnosed by isolation of *Brucella* spp. from cerebrospinal fluid (CSF), and/or the demonstration of antibodies to *Brucella* spp. in the CSF (at any titer) in the presence of any abnormality of the CSF. Epididymo-orchitis was diagnosed by swelling and

tenderness of scrotal skin, testis, and epididymis with confirmation by sonography. The hematological involvement of brucellosis includes anemia, leucopenia, and thrombocytopenia. Bronchopneumonia, pleural effusion, solitary nodules, hilar, and paratracheal lymphadenopathy, in the absence of other causes, were considered as respiratory tract involvement. Endocarditis was diagnosed by the detection of vegetations using echocardiography in the patient with anemia, elevated ESR levels, and cardiac murmur. Uveitis was accepted as ocular involvement (3).

The patients were classified into 2 sub-groups according to the presence of complications.

Statistical analysis

Data were analyzed using SPSS version 10.0. Chi-square test and Mann-Whitney U test were performed, with P-values of < 0.05 accepted as significant. Logistic regression enter method was used for multivariate analysis. Correlation was evaluated by the Spearman correlation coefficient. The diagnostic value of the CRP level for detection of complication was assessed by calculating the area under receiver operating characteristics (ROC) curve. A cut-off point was selected from the ROC curve to identify the presence of complication.

Results

A total of 324 patients were included in the study. Brucellosis was more frequent in male patients; furthermore, 180 (56%) were male and 144 (44%) patients were female. The mean age of patients was 44.0 ± 18.3 years (range 15-83 years). The possible source of infection was identified in 293 patients, 203 (62.7%) of whom had direct contact with animals or worked with animal products, and 90 (27.7%) of whom had consumed unpasteurized dairy products, especially fresh cheese. Contact with livestock was more likely in male patients (64.5%), whereas a history of ingestion of nonpasteurised products was detected in female patients (53.3%). No source was identified in the remaining 9.6% of patients. The percentage of patients with a family history of brucellosis, or presence of brucellosis cases in the surrounding area, was 36.7%.

Fifty-four percent of patients lived in rural areas, whereas 46% of patients lived in urban areas. Most of the cases were detected during the summer months and early autumn. Acute disease was found in 61.1% of patients, whereas 24.1% and 14.8% of patients had subacute and chronic forms of the disease, respectively.

Complications were detected in 142 of 324 (43.8%) cases (Table 1). Osteoarticular involvement was the

Table 1. Complications of 324 patients with brucellosis.

Complication	Acute cases	Chronic and Subacute cases	No. (%) of cases
Osteoarticular	50 (59.5)	34 (40.5)	84 (59.1)
Neurological	13 (65)	7 (35)	20 (14.1)
Urogenital*	14 (70)	6 (30)	20 (20.8)
Respiratory	4 (50)	4 (50)	8 (5.6)
Hemathologic	4 (67)	2 (33)	6 (4.2)
Ocular	1 (33)	2 (67)	3 (2.1)
Cardiovascular	1 (100)	0 (0)	1 (0.7)
Total	87 (61.2)	55 (38.7)	142 (100)

* male patients

most frequent complication, being present in 84 cases, representing 25.9% of all patients, and 59.2% of the complicated cases. Neurologic involvement was present in 20 patients, representing 6.2% of all patients. All of the neurobrucellosis cases were presented with meningitis. Twenty male patients (11.1% of all male patients) had genitourinary involvement. Respiratory, ocular, and cardiovascular

complications were the other complications. Most of the complications were detected in acute cases.

Fever, malaise, sweating, and arthralgia were the most common clinical symptoms. They were detected in 73.8%, 71%, 69%, and 52% of patients, respectively. Other clinical features of the patients are given in Table 2. Fever, splenomegaly, and hepatomegaly were the most frequent physical findings.

Table 2. Epidemiological, clinical, and laboratory features of 324 patients with brucellosis.

Characteristics	With Complications N = 142	With Complications N = 182	Total no. (%) cases	P
Gender M/F	87/55	93/89	180/144	0.068
Age	43.8 ± 17.5	44.0 ± 18.7		0.914
Age groups				
15-30	38 (26.8)	63 (34.6)	101 (31.2)	0.035
31-50	52 (36.6)	43 (23.6)	95 (29.3)	
> 51	52 (36.6)	76 (41.8)	128 (39.5)	
Occupation				
Animal husbandry	94 (66.2)	89 (48.9)	183 (56.5)	0.002
Other	48 (33.8)	93 (51.1)	141 (43.5)	
Living area				
Urban	50 (35.5)	96 (53.9)	146 (45.8)	0.001
Rural	91 (64.5)	82 (46.1)	173 (54.2)	
Possible source of infection				
Animal husbandry	102 (71.8)	101 (55.5)	203 (62.7)	0.008
Consuming raw milk	28 (19.7)	62 (34.1)	90 (27.8)	
Unknown	12 (8.5)	19 (10.4)	31 (9.6)	
Duration of symptoms				
< 2 months	87 (61.3)	111 (61.0)	198 (61.1)	0.953
> 2 months	55 (38.7)	71 (39.0)	126 (38.9)	
Clinical features				
Fever	103 (79.2)	136 (84.0)	239 (73.8)	0.298
Malaise	109 (76.8)	121 (66.5)	230 (71.0)	0.058
Sweating	104 (73.2)	120 (65.9)	224 (69.1)	0.158
Arthralgia	68 (47.9)	101 (55.5)	169 (52.2)	0.174
Chills	75 (52.8)	76 (41.8)	151 (46.6)	0.062
Back pain	68 (47.9)	78 (42.9)	146 (45.1)	0.367
Myalgia	66 (46.5)	79 (43.4)	145 (44.8)	0.581
Headache	51 (35.9)	58 (31.9)	109 (33.6)	0.444
Weight loss	45 (31.7)	49 (26.9)	94 (29.0)	0.348
Signs				
Fever	45 (32.4)	42 (24.3)	87 (26.9)	0.113
Splenomegaly	33 (23.2)	42 (23.1)	75 (23.1)	0.973
Hepatomegaly	25 (17.6)	32 (17.6)	57 (17.6)	0.996

Laboratory findings are shown in Table 3. Anemia was detected in 132 (40.7%), thrombocytopenia in 37 (11.4%), leucopenia in 36 (11.1%), and elevated CRP levels in 208 patients (64.2%). Agglutination titer was > 1/160 in 310 patients (95.7%), between 1/160 and 1/40 in 13 (4%) patients, and negative in 1 patient. Blood cultures, were positive in 118 (36.4%) out of 324 patients. *Brucella* spp. isolates were detected in 37.3% of patients with systemic involvement. The *Brucella* spp. isolation rate was highest in patients with hematologic involvement (83%). The isolation rates of *Brucella* spp. in patients with urogenital, respiratory, neurologic, and osteoarticular involvements were 50%, 50%, 35%, and 30%, respectively.

Clinical symptoms and laboratory findings of the patients with and without complications were compared (Tables 2 and 3). No statistically significant difference was found in age, or the duration of symptoms of the patients with and without complications ($P > 0.05$). When the patients were grouped according to age, the systemic involvement rate was higher in patients between 31 and 50 years of age, and this difference was statistically significant ($P = 0.035$). Although complications were observed more frequently in male brucellosis cases when compared to female patients, no statistically significant difference was detected ($P = 0.068$). Although malaise, sweating, chills, myalgia, and

headaches were detected more frequently in patients with complications, statistically significant differences were not detected between the groups ($P > 0.05$). On the other hand, dealing with animal husbandry, living in a rural area, and elevated CRP levels were significantly associated with complications formed by univariate analysis ($P < 0.05$). The median level of CRP in patients without system involvement was 1.2 mg/dL, whereas the value for the patients with system involvement was 2.3 mg/dL. The median levels of CRP values in patients with hematologic, urogenital and osteoarticular involvements were as follows: 9.6 mg/dL, 7.9 mg/dL, and 2.5 mg/dL, respectively. When CRP levels were evaluated according to the duration of symptoms, median CRP levels were 5.3 mg/dL, 3.4 mg/dL, and 4.5 mg/dL in acute, subacute, and chronic cases, respectively.

By multivariate analysis, elevated CRP levels remained independently associated with systemic involvement ($P < 0.05$). A correlation was found between the serum CRP level and presence of complications ($r = 0.146$, $P = 0.009$). The diagnostic value of the serum CRP level for systemic involvement was assessed by the area under the ROC curve (AUROC at 0.58, 95% CI 0.52-0.65). Based on AUROC, 3.5 mg/dL was calculated as a cut-off point to predict complications in brucellosis patients. The sensitivity and specificity of this cut-off value were 44% and 70%, respectively.

Table 3. Laboratory features of Brucellosis patients with and without complications.

Findings	Complicated N = 142	Noncomplicated N = 182	Total no. (%) cases	P
White blood cell				
< $4.5 \times 10^3/\text{mm}^3$	17 (11.1)	19 (11.1)	36 (11.1)	0.684
$4.5-11 \times 10^3/\text{mm}^3$	119 (83.8)	158 (86.8)	277 (85.5)	
> $11 \times 10^3/\text{mm}^3$	6 (4.2)	5 (2.7)	11 (3.4)	
Anemia	66 (46.7)	66 (36.2)	132 (40.7)	0.060
Thrombocytopenia	19 (12.7)	18 (10.4)	37 (11.4)	0.651
ALT elevation	37 (26.1)	50 (27.5)	87 (26.9)	0.775
AST elevation	34 (23.9)	48 (26.4)	82 (25.3)	0.618
Elevated ESR	101 (71.1)	125 (68.7)	226 (69.8)	0.634
Elevated CRP	101 (71.1)	107 (58.8)	208 (64.2)	0.022
Positive blood culture	53 (37.3)	65 (35.7)	118 (36.4)	0.765

Discussion

It is important to determine the epidemiological features of the illness for the control of the infection. Brucellosis is an important health problem in this country, with numerous reports of cases from different regions(4-7).

Three hundred twenty-four brucellosis patients were evaluated in this study. The majority of our patients lived in rural areas and had direct contact with animals, or worked with animal products. Consumption of fresh cheese prepared with unpasteurized milk was the second important epidemiological feature for the acquiring of infection. The distribution of risk factors in our series was different from that of Hasanjani et al. (8), who reported that only a small percent of patients (11.3%) could be linked to a common risk factor such as working with animals. As previously reported, we observed the prevalence of brucellosis to be higher in male patients (9,10). A family history of brucellosis was detected in approximately one-third of our patients. This could be due to sharing the same environment, livestock contact, and dairy product consumption as reported by Almuneef et al. (11).

Symptoms suggesting brucellosis are protean and nonspecific, yet commonly include fever, chills, sweating, headache, fatigue, arthralgia, back pain, myalgia, and weight loss (12,13). The physical findings included fever in 80%-90% of the patients and hepatosplenomegaly in 20%-30%, lymphadenopathy 8%-25%, and osteoarticular findings in 12%-43% from different studies (12-14). Routine laboratory tests are usually unremarkable or nonspecific. The frequency of symptoms, signs and laboratory findings in our patients were similar to those reported in the literature (5,7,12-15).

Brucellosis is a systemic infection in which any organ or system can be involved. When involvement of a specific organ predominates, the disease is often termed focal or complicated. However, it is always difficult to determine what is a complication, and what is considered an expected manifestation (3). The complication rate of brucellosis varies between 27.7% and 49% in large surveys (5,9,12,15,16). Our rate was 43.8%, which was near the top of the previously reported rates. Our hospital is a tertiary care hospital in the Central Anatolia region; uncomplicated cases

were treated in their hometown, whereas most patients with complications were referred to us, which might be the cause of our relatively high incidence rate.

Osteoarticular involvement such as sacroiliitis, spondylitis, and arthritis are the most frequent focal complications, with a frequency of 21% to 37.5% (5,12,17-19). Similar to previous studies, osteoarticular manifestations were found to be 25.9% in our patients.

Neurologic involvement was reported in 3% to 5% in most studies, but may mount up to 17.8% in endemic areas (20-23). Clinical manifestations of neurobrucellosis vary widely, in which meningitis is the most frequent manifestation (3). Neurologic complications were detected in 6.2% of our patients. All of them had meningitis as previously reported (24). Unilateral epididymo-orchitis is a common genitourinary complication in men (23). We detected epididymo-orchitis in 11.1% of male brucellosis patients that were reported previously (25). Lobar pneumonia, bronchitis, pulmonary nodules, hilar adenopathy, and pleural infection all have been reported as respiratory complications of brucellosis (3,12,26). Pulmonary involvement was noted in 2.5% of our patients.

In our study, animal husbandry and living in rural area were found as significant findings for the existence of complications in brucellosis by univariate analysis, but not in multivariate analysis. For people living in rural areas of Turkey, animal related jobs such as animal raising are the main way to earn their living. It is known that people involved in animal husbandry are at an increased risk of contracting brucellosis (3). That is compatible with our multivariate analysis result.

There is no definitive means of predicting which brucellosis patients will develop complications. However, in a study by Colmenero et al. (12) diagnostic delay, elevated sedimentation rates, and elevated alpha-2 globulin levels correlated with the development of focal complications. We found no difference in sedimentation rates and the duration of symptoms as risk factors for complications. However, we found elevated CRP levels greater than 3.5 mg/dL were associated with the presence of complications. Although the serum CRP levels is a nonspecific marker of inflammation, it was thought that using a

new cut-off value for CRP levels could help the physician in further investigation of the complications. CRP levels were found to be higher in hematological and urogenital complication groups. When each complication was evaluated according to the CRP cut-off levels in hematological and urologic complication groups, 83% and 75% of patients have higher levels of CRP. Although the skeletal involvement was the most frequent complication, the median CRP level in this group was only moderately high. Although Al-Kassab et al. reported lower levels of CRP in osteoarticular involvement of brucellosis, elevated CRP levels were expected in the complicated

cases, and our results supported this finding (27). In a previous study from our center, elevated CRP levels were associated with complications in brucellosis (28).

The complications of brucellosis may cause high morbidity. It may be useful to identify the possible indicator or indicators that are associated with the complicated form of the disease for early diagnosis and appropriate treatment. In our study, an elevated CRP level was found as a significant marker in patients with complications. In conclusion, elevated CRP levels, in accordance with clinical manifestations of the patient, may be a sign of complications, and needs further investigation.

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