Diagnostic clues for spondylitis in acute brucellosis

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ABSTRACT

الأهداف: .تهدف هذه الدراسة إلى تحديد العوامل التي تؤثر في تشخيص التهاب الفقار البروسيلات.

الطريقة: تضمنت هذه الدراسة الإستعادية 277 مريض مصاب بداء البروسيلات اقرت عيادات مستشفى أديامان ومستشفى أديامان 82 سنة للأمراض المعدية والأحياء الدقيقة السريرية ، أديامان، تركيا خلال الفترة ما بين يناير2010 م وديسمبر2012م.تم تشخيص داء البروسيلات الحاد بواسطة اختبارSTA ونمو *Brucella spp.* أعد بشكل مناسب لمستنبتات(bactec). تم تشخيص التهاب الفقار البروسيلات ومتابعتها مع تعزيزالتباين التصويري بالرنين المغناطيسي.

النتائج: من بين مجموع 227 مريض مصاب بداء البروسيلات، كان عدد المرضى من الذكور 88 (38.8%) وعدد المرضى من الإناث 139 (61.2%). تم اكتشاف التهاب الفقار البروسيلات في 54 (23.7%) مريض.لدى مرضى التهاب الفقار البروسيلا متوسط عالي من العمر وارتفاع درجة الحرارة وزراعة الدم بمعدل ايجابي مقارنة مع مرضى البروسيلات. اظهر تحليل الإنحدار اللوجستي أن الذكور(OR:3.006)، أكبر سناً (OR:1.025)، ESR (OR:1.067)، وارتفاع درجة الحرارة عند وقت القبول (OR: 2.550)، وزراعة الدم الإيجابي لأنواع البروسيلات *Brucella spp.* (OR:4.003)ارتبطت القيم بشكل مستقل مع التهاب الفقار البروسيلات. ووجدوا أن ارتفاع مستوىCRP (OR:0.971) ليس عامل خطر لإلتهاب القفار البروسيلي.

الخاتمة: وفقاً لنتائج الدراسة، يزداد خطر الإصابة بإلتهاب الفقار البروسيلات في مرضى كبار السن الذي يعانون من داء البروسيلات الحاد والذين يعانون أيضاً من ارتفاع درجة الحرارة و *Brucella spp* تزداد زراعة الدم عند الذكور الذين لديهم معدل عال من ترسيب كريات الدم الحمراء ESR.

Objectives: To determine the diagnostic factors for brucellar spondylitis.

Methods: This retrospective study included 227 consecutive brucellosis patients admitted to the Infectious Diseases and Clinical Microbiology clinics of Adiyaman State Hospital and Adiyaman 82nd Year State Hospital, Adiyaman, Turkey between January 2010 and December 2012. Acute brucellosis was diagnosed by standard tube agglutination test, and/or growth of *Brucella spp.* in appropriately prepared culture media (Bactec). Brucellar spondylitis was diagnosed and followed-up with contrast-enhanced magnetic resonance imaging.

Results: Among the 227 brucellosis patients included, 88 (38.8%) were male, and 139 (61.2%) were female. Brucellar spondylitis was detected in 54 patients (23.7%). Brucellar spondylitis patients had higher mean age, higher fever, and higher blood culture positivity rate when compared with brucellosis patients (p=0.001, p=0.001, and p=0.001). Logistical regression analysis determined that male gender (OR: 3.006), older age (OR: 1.025), erythrocyte sedimentation rate (ESR) (OR: 1.067), high fever at the time of admission (OR: 2.550), and positive blood cultures for *Brucella spp.* (OR: 4.003) values were independently associated with brucellar spondylitis. However, high C-reactive protein (CRP) levels (OR: 0.971) were not found as a risk factor for brucellar spondylitis.

Conclusions: The results of this study shows that the risk of developing brucellar spondylitis is high in patients with acute brucellosis, who are at advanced age, who have high fever, that have *Brucella spp.* growth in their blood culture that has a high ESR value, and who are male.

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Brucellosis is a chronic granulomatous infection caused by *Brucella spp*, which is normally treated with a combination of antibiotics; and if untreated, it may lead to clinical morbidity, and loss of productivity. Prevalence of brucellosis is high in certain geographic areas, such as the Mediterranean countries.[1] Seropositivity among the Turkish population was 2-6% at various time periods in different risk groups.[2,3] After ingestion of *Brucella spp*, one third of the invading organisms survives in phagolysosomes, which create a unique site for bacterial growth and immune escape. In its unique shelter, *Brucella spp.* may persist for long periods and cause chronic complications. Prolonged antibiotic treatment is required for eradication due to the difficulty of diffusion into phagolysosomes.[1] Brucellosis is known as a "great imitator" of infectious diseases due to its various clinical presentations. Focal involvement is found in 36.1% of patients, most commonly as osteoarticular involvement.[4] Osteoarticular involvement can be seen in acute, or chronic, or relapsed brucellosis. Brucellar spondylitis, which was once described as "one of the most incapacitating and painful maladies that can afflict man," presents in 10-21.4% of patients,[1] and may cause diagnostic obstacles in both high and low endemic countries.[5-7] Brucellar spondylitis symptoms are initially subtle and non-specific, and any delays in diagnosis and treatment may lead to morbidity.[8] There is currently not enough data available to discriminate between patients with brucellosis and brucellar spondylitis, regarding clinical and laboratory findings. This study aims to determine the diagnostic factors for brucellar spondylitis.

Methods. This retrospective study involved 227 consecutive acute brucellosis patients admitted to the Infectious Diseases and Clinical Microbiology clinics of Adiyaman State Hospital and Adiyaman 82nd Year State Hospital between January 2010 and December 2012. This work was carried out in accordance with the Helsinki Declaration. Approval was obtained from the ethical committee of Adiyaman University. Age, gender, occupation, route of transmission, laboratory culture results, and treatment protocols were recorded in patient follow-up sheets. Acute brucellosis was diagnosed if the standard tube agglutination (STA) test titer was 1/160 or higher, or if there was a 4-fold rise in titer between 2 STA tests performed 2 weeks apart in the presence of clinical symptoms (a compatible clinical presentation such as arthralgia, fever, sweating, chills, headache, and malaise) within the previous 8 weeks, and/or growth of *Brucella spp*. in appropriately prepared culture media (Bactec). Patients included in the study met the definition of acute brucellosis, were 18 years old or older at the time of the study initiation, had not been previously diagnosed with or treated for brucellosis, did not have an accompanying immunosuppressive condition, and were not pregnant. Brucellar spondylitis was diagnosed and followed-up with contrast-enhanced MRI. An MRI was performed on all patients with low back pain, and brucellar spondylitis was diagnosed as defined by Pourgbaher et al.[9]

Data were analyzed using the Statistical Package for Social Sciences version 18.0 (SPSS Inc, Chicago, IL, USA) Chi square test was used in the analysis of cathegorical analysis, and independent sample t-test was used in the analysis of continuous variables. In order to identify the risk factors associated with spondylitis, stepwise logistic regression analysis was carried out. Age, STA, alanine aminotransferase (ALT), aspartate aminotransferase (AST), erythrocyte sedimentation rate (ESR), leucocyte count (WBC), C-reactive protein (CRP), fever, malaise, and blood culture positivity were included in the initial logistic regression model. Odds ratio (OR) and 95% confidence interval (CI) were measured at the end of logistic regression analysis. A $p<0.05$ was considered statistically significant.

Results. Among the 227 brucellosis patients, 88 (38.8%) were male, 139 (61.2%) were female, and mean age was 43.1±15.2 years. Route of transmission was identified in 98.7% of patients; the most common route (79.1%) was the consumption of fresh cheese made from raw milk, followed with contact with livestock (19.6%). The 3 most frequent symptoms were arthralgia, anorexia, and malaise.

Laboratory parameters, clinical symptoms, and physical examination findings of acute brucellosis cases are summarized in **Table 1**. Laboratory tests revealed anemia in 27.3%, thrombocytopenia in 14.1%, and leucopenia in 10.6% of patients. The CRP was elevated in 167 patients (mean CRP value: 23.7±21.7 mg/l), and ESR in 136 patients (mean ESR value: 30.1±20.1 mm/hours). Brucellar spondylitis affected the lumbar, thoracic, and cervical vertebrate in descending order was the most common form. Focal manifestations were found in 75 patients; among those, brucellar spondylitis was detected in 54 (23.7%) patients, and sacroiliitis in 21 (9.2%) patients. Neurobrucellosis was diagnosed in one patient (0.45%). Characteristics, symptoms, and changes in laboratory values of patients with brucellar spondylitis and brucellosis are shown in **Table 2**. Brucellar spondylitis patients had higher mean age ($p=0.001$), higher fever ($p=0.001$), and higher blood culture positivity rate ($p=0.001$) when compared with

Table 1 - Clinical symptoms, physical examination findings and laboratory parameters of 227 acute brucellosis cases.

Parameters	Number of cases (%)
Clinical symptoms	
Arthralgia	193 (85.0)
Anorexia	169 (74.4)
Malaise	157 (69.2)
Night sweating	149 (65.6)
Fever	119 (52.4)
Low back pain	64 (28.2)
Weight loss	56 (24.6)
Clinical signs	
Hepatomegaly	56 (24.6)
Splenomegaly	32 (14.1)
Lymphadenopathy	3 (1.3)
Laboratory	
Leucopenia (4.000/mm^3)	24 (10.6)
Leucocytosis (10.000/mm^3)	5 (2.2)
Anemia (Hgb<10 g/dl)	62 (27.3)
Thrombocytopenia (Plt <150.000/mm^3)	32 (14.1)
ALT >40 u/L	59 (25.9)
AST >40 u/L	67 (29.5)
CRP (>5mg /dl)	167 (73.5)
ESR (>20 mm/h)	136 (59.9)
Spondylitis	54 (23.7)
Lumbar localization	49 (90.7)
Cervical localization	1 (1.9)
Thoracic localization	4 (7.4)

Hgb - hemoglobin, Plt - platelet, ALT - alanine aminotransferase, AST - aspartat aminotransferase, CRP - C-reactive protein, ESR - erythrocyte sedimentation rate

brucellosis. Risk factors associated with spondylitis are shown in **Table 3**. Logistical regression analysis determined that ESR (OR: 1.067), high fever at the time of admission (OR: 2.550), older age (OR: 1.025), male gender (OR: 3.006), and positive blood cultures for Brucella spp. (OR: 4.003) values were independently associated with brucellar spondylitis. However, high CRP levels (OR: 0.971) were not found as a risk factor for brucellar spondylitis.

Discussion. Brucellosis causes diagnostic and therapeutic challenges due to its similarities to other diseases regarding clinical presentation. Among the focal manifestations, osteoarticular involvement constitutes most of complications. Brucellar spondylitis is a challenging diagnosis particularly in low endemic areas; delayed diagnosis and inappropriate treatment may lead to prolonged morbidity.[8] Relatively expensive techniques, such as contrast enhanced MRI[9,10] and bone scintigraphy[11] can be utilized for diagnosis, however, there is a lack of useful and cheaper methods in the outpatient setting. This report aimed to determine diagnostic clues to aid treatment in an outpatient setting. This study showed again, that osteoarticular involvement is the most common manifestation of

Table 2 - Characteristics, symptoms and changes in laboratory values of patients with brucellar spondylitis and brucellosis.

Variables	Brucellosis patients (n=173)	Brucellar spondylitis (n=54)	*P*-value
Gender (male/female)	56 (32.4)/117 (67.6)	32 (59.3)/22 (40.7)	0.005
Age (mean±STD)	42.9±14.6	50.8±17.9	0.001
High fever (%)	108 (62.4)	46 (85.1)	0.001
Malaise (%)	137 (79.1)	43 (79.6)	0.126
Night sweating (%)	145 (83.8)	45 (83.3)	0.121
Blood culture positivity (%)	19 (10.9)	17 (31.5)	0.001
Brucella STA (median, min-max)	1/320 (1/160-1/5120)	1/640 (1/80-1/2560)	0.331
ALT (u/L, mean±STD)	28.6±13.2	29.3±17.2	0.762
AST (u/L, mean±STD)	30.4±14.9	30.5±16.0	0.958
CRP (mg/dl, mean±STD)	22.1±20.3	24.2±32.8	0.573
ESR (mm/h, mean±STD)	28.5±19.3	55.4±27.4	0.001
WBC (/mm^3, mean±STD)	7223.1±2346.8	7381.4±3286.2	0.686

ALT - alanine aminotransferase, AST - aspartate aminotransferase, CRP - C-reactive protein, ESR - erythrocyte sedimentation rate, WBC - leucocyte count

Table 3 - Risk factors associated with brucellar spondylitis.*

Variables	Beta factor (B)	Standart Error (S.E)	*P*-value	Odd's ratio	95% confidence intervals
ESR	0.065	0.012	0.001	1.067	1.043-1.092
Older age	0.025	0.013	0.050	1.025	1.001-1.051
Male gender	1.101	0.407	0.007	3.006	1.354-6.674
Fever at admission	0.936	0.474	0.048	2.550	1.008-6.450
Positive blood cultures for *Brucella spp*.	1.387	0.487	0.004	4.003	0.540-10.405

*Forward stepwise logistic regression analyze. ESR - erythrocyte sedimentation rate

brucellosis. Brucellar spondylitis and sacroiliitis were present in 23.7% and 9.2% of acute brucellosis patients, contrary to the present results by Kokoglu et al[12] and Turan et al,[13] which demonstrated that sacroiliitis was twice as common than brucellar spondylitis in brucellosis patients. It is noted that patient characteristics varied between the present study and those of Kokoglu et al[12] and Turan et al,[13] the former included only acute cases, whereas the latter included chronic brucellosis cases. Differences in the diagnostic tools used might have also contributed to the discrepancy between the studies. The MRI and bone scintigraphy are the most efficient and sensitive instruments in the diagnosis of brucellar spondylitis. Contrast-enhanced MRI was performed for all possible/probable cases in the present study, which boosted the sensitivity of the findings. It has been stated that brucellar spondylitis is a late complication of brucellosis;[14] however, it has also been demonstrated that brucellar spondylitis can present during acute infection.[4,15,16] This corroborates the current findings that brucellar spondylitis is not a late complication of brucellosis, and can also be diagnosed in acute cases. The results herein showed that older age, male gender, fever at the time of admission, higher blood culture positivity rate, and higher ESR values are the major diagnostic clues suggestive of brucellar spondylitis. Hashemi et al[8] showed that chills, low back pain, splenomegaly, and hepatomegaly were more prevalent in patients with osteoarticular involvement. Turan et al[13] found that hepatomegaly, splenomegaly, and lumbar, and sacroiliac joint pain were more common in brucellar spondylitis patients when compared with brucellosis cases, however, they could not demonstrate any difference in hematological and biochemical values. No association between back pain and the clinical form of brucellosis was observed in the present study despite many patients were suffering from back pain. Discrimination between pain due to brucellosis, and pain due to other etiologies could not be established. Fever, back pain, and constitutional symptoms (that is; nocturnal sweating, loss of appetite, weakness) were common in brucellar spondylitis patients.[14,15] Colmenaero et al[17] reported moderately increased ESR and higher blood culture positivity in patients with osteoarticular complications. Blood cultures in the study by Turunc et al[15] yielded *Brucella spp.* in 56.2% of patients, and a high rate of microbial isolation was ascribed to most patients with acute brucellosis at the time of diagnosis. Our results are in accordance with these studies. The higher rate of blood culture positivity in spondylitis patients may also be due to increased hospitalization of these patients, and routine collection of blood samples for cultivation prior to antibiotic treatment; we did not draw blood samples from outpatients. We considered the reason for the frequent occurrence of brucellar spondylitis in the presence of fever was associated with the hematogenous spread during bacteriemia, and the increase in this risk at advanced age was associated with the age-related immunosuppression. However, the reason for frequent occurrence of brucellar spondylitis in male gender could not be explained. We also did not find any information on this issue during our literature searches. High CRP was not found as a risk factor for brucellar spondylitis in our study. Looking at the studies on this subject, it is seen that high CRP has not been assessed as a risk factor for developing brucellar spondylitis in any of them.[18-22]

Brucellosis can present at any age.[4] However, brucellar spondylitis was thought to be more common in older patients.[18] Turunc et al[15] and Hashemi et al[8] could not demonstrate any age difference between brucellar spondylitis and brucellosis patients. In this study, patients with brucellar spondylitis were older than those with brucellosis. Furthermore, older age was shown to be an independent risk factor for brucellar spondylitis. Mechanisms underlying the pathogenesis of this infection in the older age group need to be investigated. Brucellosis can affect both genders equally. However, a slight female dominance was found in some studies,[4] while other studies could not demonstrate any difference among males and females.[19] In this study, we detected a female dominance in acute brucellosis cases (88 versus 139 patients). Having a single center design instead of multicentric design, including limited number of spondylitis patients and composing of acute brucellosis patients are the main limitations of this study. Although brucellosis has been eradicated from a number of developed countries, it continues to be a major public and animal health problem in many regions of the world.[2] It can present with varying clinical symptoms. Early diagnosis and treatment are important to avoid further complications, morbidities, and loss of function. Our results show that patients with acute brucellosis who are at advanced age, who have high fever, that have *Brucella spp.* growth in their blood culture, that have a high ESR value, and who are male should be closely monitored for brucellar spondylitis. Further studies are needed to identify additional risk factors in the diagnosis of focal brucellosis.

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