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Clinical appearance of brucellosis in adults: fourteen years of experience

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Aim: To indicate the clinical course and results of brucellosis in our region during the recent years, and to compare these findings to the literature.

Materials and methods: This study was based on a review of the medical records of adult patients older than 14 years who were followed with the diagnosis of brucellosis from March 1997 to October 2010.

Results: Included in this analysis were 317 patients, including 136 males (43%), with an average age of 40 ± 17 years. In 66 patients (21%), reproduction of *Brucella* was identified in the blood. Of the patients, 61% were identified as having the acute form, 35% the subacute form, and 4% the chronic form. Arthralgia, fever, weight loss, sacroiliitis, and spondylitis were the most frequent symptoms and findings accompanying the disease. There was a significant relationship between advanced age and the development of both spondylitis and arthritis (P = 0.000 and P = 0.028, respectively). Furthermore, there was a significant relationship between a high erythrocyte sedimentation rate and the presence of spondylitis, sacroiliitis, and visceral abscesses (P = 0.001, P = 0.013, and P = 0.049, respectively).

Conclusion: This study provides a review of the disease and its complications. Osteoarticular involvement, and particularly the presence of spondylitis in patients and the complications in elderly patients, should be studied. Laboratory parameters, the patient's age, and the duration of symptoms may help to identify complicated cases.

Key words: Brucellosis, complication, clinical course

Erişkinlerde brusellozun klinik görünümü: Ondört yıllık deneyim

Amaç: Bu çalışma, son yıllarda bölgemizde brusellozun klinik seyri ve sonuçlarını göstermek ve literatür ile karşılaştırmak amacı ile planlanmıştır.

Yöntem ve gereç: Çalışma, Mart 1997-Ekim 2010 tarihleri arasında bruselloz tanısı alan erişkin hastaların tıbbi kayıtları baz alınarak yapılmıştır.

Bulgular: Analiz, yaş ortalaması 40 ± 17 olan 136'sı erkek (% 43) 317 hastayı içermiştir. Hastaların 66'sında (% 21) kan kültüründe *Brucella* üredi. Yüzde 61 hastanın hastalığın akut, % 35 hastanın subakut ve % 4 hastanın ise kronik formunda olduğu belirlendi. Artralji, ateş, kilo kaybı, sakroileit ve spondilit, en sık karşılaşılan semptom ve bulgular olarak belirlendi. İleri yaş ile spondilit ve artrit gelişimi arasında anlamlı ilişki saptanmıştır (sırasıyla P = 0,000 ve P = 0,028). Yine, yüksek ESR düzeyi ile spondilit, sakroileit ve viseral apse arasında anlamlı ilişki saptanmıştır (sırasıyla P = 0,001, P = 0,013 ve P = 0,049).

Sonuç: Çalışma hastalığın seyri ve komplikasyonlarınınyeniden gözden geçirilmesini sağlamıştır. Hastalarda osteoartiküler tutulum, özellikle spondilit varlığı ve ileri yaştaki hastalarda komplikasyonlar araştırılmalıdır. Laboratuvar parametreleri, hasta yaşı ve semptom süreleri, komplike olguları belirlemede yardımcı olabilir.

Anahtar sözcükler: Bruselloz, komplikasyon, klinik seyir

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Introduction

Brucellosis is an important zoonotic disease that can occur globally, and it is generated by the facultative anaerobic *Brucella* species. It is a systemic disease that has the potential to spread to all of the organs (1). Involvement of bones and/or joints is the most frequent complication, and its incidence in different series has been reported as 10%-85% (2,3). Incidence of involvement of the vertebrae in brucellosis is 2%-54%, and such cases involve difficulty of treatment and nonstandardized treatment periods. The treatment may fail or the disease may relapse despite the application of a therapy. Aminoglycosides and fluoroquinolones may be added to the standard treatment regime (doxycycline + rifampicin) (1-3).

The disease leads to significant economic losses in numerous developing countries due to its high morbidity, both in humans and in animals, and it stands out as a serious public health issue. In general, the clinical appearance of the disease may change over the years as a result of early and advanced diagnosis methods and the developing consciousness of the public of healthcare. However, in countries and rural areas where the disease is endemic, there may be cases in which diagnostic advantages are not accessible or healthcare services are not implemented accurately and properly. Moreover, the success or failure in practices of animal healthcare affects the epidemiology of the disease. In our unit, a retrospective assessment of 238 patients over 8 years, published in 1998, demonstrated that the disease is most common among young adults without discrimination of sex, and it progresses with osteoarticular involvement at a significant rate (3). This study was planned to indicate the clinical course and results of brucellosis in our region during the recent years and to compare these findings to the literature.

Materials and methods

This study was based on a review of the medical records of adult patients older than 14 years who were followed with the diagnosis of brucellosis from March 1997 to October 2010 at Çukurova University's Hospital of the Faculty of Medicine, which offers third-step healthcare services. The demographic data, diagnosis of the disease, course, treatment, and termination data of the patients were recorded. Clinical properties including fever, weight loss, arthralgia, arthritis, sacroiliitis, spondylitis, epididymo-orchitis, neurological involvement, hepatomegaly, splenomegaly, and visceral abscess, and laboratory parameters including initial white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels were obtained. The treatment regimes, treatment periods, and termination information of the patients were evaluated.

Brucellosis was diagnosed by *Brucella* tube agglutination titration of ≥1/160 and/or the reproduction of *Brucella* species in blood culture, as well as by relevant symptoms and findings. In the Wright agglutination test, the serum dilution was conducted between 1:20 and 1:2560. Blood culture samples were treated for 14 days in a BACTEC 9240 system (Becton-Dickinson, Maryland, USA). The reproducing gram-negative coccobacillus was identified by conventional biochemical tests (motility, oxidase, catalase, and glucose fermentation).

The disease was divided into 3 forms based on the duration of symptoms. It was defined as acute if the symptom period was less than 2 months, subacute if ranging from 2 months to 1 year, and chronic if longer than 1 year (1).

Peripheral arthritis was defined as swelling, rash, and limited movement of the involved joints, and sacroiliitis was defined as sclerosis and narrowing of joint spacing identified in radiography and/or tomography. Epididymo-orchitis was defined as swelling and pain in the scrotal dermis, testis, and epididymis regardless of ultrasonographic findings (1).

The diagnosis of sacroiliitis was evaluated by direct findings of plain radiography and bone scintigraphy (1).

Diagnosis of neurobrucellosis was established through specific antibodies in the cerebrospinal fluid (CSF) and/or *Brucella* species in the CSF (1).

The patients received doxycycline + rifampicin or other combination therapies for 6 weeks. In cases that progressed with complications (spondylitis, neurobrucellosis, etc.), treatment was planned for 3 months and a time to be specified according to the radiological and clinical recovery follow-up. Other

medicines such as quinolones, aminoglycosides, and trimethoprim-sulfamethoxazole in combination were applied in treatment considering the adverse effects, intolerance, or other host factors.

Termination was defined as recovery, sequel, or relapse. Recovery was defined as complete correction of the disease and its symptoms, sequel was defined as continued pain symptoms at least 6 months after the treatment along with functional constraints on movement or abnormal findings during physical examination, and relapse was defined as observation of anincrease in the serological titration and/or positive culture and disease symptoms and findings during the follow-up period. The 6-month observations of the patients were used for assessment (1).

Statistics were performed using SPSS version 11.5. Descriptive statistics were used for demographic variables. Student's t-test was used for quantitative variables, and Pearson's chi-square test and Fisher's exact test were performed for categorical variables. $P < 0.05$ was considered to be statistically significant.

Results

There were 425 cases of brucellosis during the study period; however, only the data of 317 patients, including 136 males (43%), were included in the analysis. The average age of the patients was 40 ± 17 years, the median age was 38 years (14-88), and the clinical and laboratory properties of the patients are provided in Tables 1 and 2, respectively.

In 301 patients (95%), the tube agglutination test was positive at 1:160 and above. In 66 patients (21%), reproduction of *Brucella* was identified in the blood.

There were no statistically significant differences between the sexes and the symptoms and clinical findings. When the ages and findings of the patients were compared, there was a statistically significant relationship between elderly age and the development of both spondylitis and arthritis (P = 0.000 and P = 0.028, respectively). Moreover, the frequency of splenomegaly and neurobrucellosis among the young population was found to be high, which was statistically significant (P = 0.005 and P = 0.001, respectively) (Table 3).

Table 1. Clinical properties of patients.

Clinical properties	n (%)
Fever	221 (69.7)
Arthralgia	249 (78.5)
Weight loss	91 (28.7)
Hepatomegaly	48 (15.1)
Splenomegaly	39 (12.3)
Sacroiliitis	86 (27.1)
Unilateral	46
Bilateral	40
Peripheral arthritis	13 (4.1)
Spondylitis/spondylodiscitis	72 (22.7)
Epididymo-orchitis*	10 (7.4)*
Meningoencephalitis/meningitis	12 (3.8)
Visceral abscess	16 (5)

*This calculation was conducted only for male patients.

The disease symptom period was evaluated in 251 patients. Of the patients, 61% were identified as having the acute form, 35% the subacute form, and 4% the chronic form. There was no statistically significant difference between ages and sex across the forms. The comparison of symptoms and findings across the forms is evaluated in Table 4.

In cases of spondylitis, the most common (approximately 85%) involvement was of the lumbar vertebrae (sum of lumber, lumbosacral, and thoracolumbar involvement). Sacroiliitis was identified in 32% of the spondylitic cases and 26% of nonspondylitic cases (P = 0.296). The involvement

Table 2. Laboratory properties of patients.

Laboratory properties	Average ± standard deviation	(Minimum-maximum)
WBCs (count/mm^3)	6836 ± 2613	1400-15,600
CRP (mg/L)	35 ± 42	2-303
ESR (mm/h)	33 ± 25	2-120

Table 3. Comparison of ages and clinical properties of patients.

Properties	Yes No	Number	Average age ± standard deviation	P-value**
Spondylitis	Yes	72	53.40 ± 14.5	0.000
	No	245	35.7 ± 15.9	
Visceral abscess	Yes	16	47.6 ± 15.4	0.060
	No	301	39.3 ± 17.2	
Hepatomegaly	Yes	48	37.2 ± 17.5	0.276
	No	269	40.2 ± 17.3	
Splenomegaly	Yes	39	32.5 ± 16.4	0.005
	No	278	40.7 ± 17.1	
Neurobrucellosis	Yes	12	26.4 ± 11.3	0.001
	No	305	40.3 ± 17.3	
Arthritis	Yes	13	50 ± 17.5	0.028
	No	304	39.3 ± 17.1	
Arthralgia	Yes	249	39.9 ± 17	0.782
	No	68	39.2 ± 18.2	
Fever	Yes	221	39.1 ± 16.7	0.360
	No	96	41 ± 18.5	
Sacroiliitis	Yes	86	39.8 ± 18.1	0.979
	No	231	39.7 ± 17	
Epididymo-orchitis*	Yes	10	41 ± 14.7	0.815
	No	126	39.6 ± 17.9	

*This calculation was conducted only for male patients.
**Fisher's exact test was used.

characteristics of the vertebrae in spondylitic cases are presented in Table 5.

When the laboratory parameters of the patients and the relationship between complicated forms of brucellosis were compared, there was a statistically significant relationship between high ESR and the presence of spondylitis, sacroiliitis, and visceral abscesses (P = 0.001, P = 0.013, and P = 0.049, respectively). Furthermore, there was a significant relationship between the presence of fever and hepatomegaly and a high ESR (P = 0.001 and P = 0.012, respectively). The CRP value was found to be high at a statistically significant level in cases of neurobrucellosis and spondylitis (P = 0.000 and P = 0.009, respectively). The WBC value, despite being at regular limits, was found to be lower in cases with arthralgia and splenomegaly (P = 0.009 and P = 0.0012, respectively) (Table 6).

Table 4. Comparison of patient properties based on brucellosis phase.

Properties	Disease phase		
	Acute form (n = 153)	Subacute form (n = 87)	Chronic form (n = 11)
Age (years), median (min-max)	36 (14-88)	38.5 (14-76)	45 (16-68)
WBC (count/mm^3), median (min-max)	6600 (1400-17,500)	6600 (2400-14,200)	5800 (4700-10,000)
CRP (mg/L), median (min-max)	22 (2-121)	20 (2-141)	11 (3-65)
ESR (mm/h), median (min-max)	30 (2-111)	24 (2-120)	8 (2-60)
Sacroiliitis, n (%)	27 (17.9)	17 (19.8)	4 (36.4)
Spondylitis, n (%)*	23 (15.2)	37 (43)	4 (36.4)
Visceral abscess, n (%)**	3 (2)	12 (14)	0 (0)
Hepatomegaly, n (%)	24 (15.9)	9 (10.5)	0 (0)
Splenomegaly, n (%)	26 (17.2)	9 (10.5)	0 (0)
Neurobrucellosis, n (%)	8 (5.3)	3 (3.5)	1 (9.1)
Epididymo-orchitis, n (%)[&]	6/72 (16.6)	3/36 (8.3)	0/4 (0)
Arthritis, n (%)	2 (1.3)	3 (3.5)	0 (0)
Arthralgia, n (%)	123 (81.5)	68 (79.1)	9 (81.8)
Fever, n (%)***	117 (77.5)	59 (68.6)	5 (45.5)
Weight loss, n (%)	54 (35.8)	30 (34.9)	1 (9.1)

*P = 0.00, **P = 0.001, and ***P = 0.037; [&]only in male patients (Pearson's chi-square test was used).

Table 5. Characteristics of spondylitis.

Properties	n* (%)
Number of spondylitis cases	72 (22.7)
Involved vertebral region**	
Lumbar	47 (65.3)
Thoracolumbar	7 (9.7)
Lumbosacral	7 (9.7)
Thoracal	6 (8.3)
Cervical	3 (4.2)
Cervicothoracic	2 (2.8)
Number of involved vertebrae	Median: 2 (1-11) Average: 2.84 ± 1.946
Presence of abscess**, ***	
Paraspinal abscess	16 (22.2)
Epidural abscess	11 (15.3)
Sacroiliitis in spondylitic cases*	23 (32)

*n = 317, **percentages were based on 72 patients, ***4 patients had both paraspinal and epidural abscesses.

The treatments of the patients are summarized in Table 7. Of the patients, 272 (87%) used dual antibiotherapy, and 45 patients (13%) used triple antibiotherapy. In their treatment regimes, 27 (8.5%) of the patients used quinolone, and 33 (10.4%) used aminoglycoside. Use of aminoglycoside was found to be high at a statistically significant level, particularly in the presence of spondylitis (P = 0.000). Furthermore, there were no statistically significant relationships between the clinical findings and the use of aminoglycoside and quinolone. The patients were treated for an average of 92 ± 97.8 days and a median of 45 (7-730) days.

As 77 of the patients (24.3%) did not show up for follow-up after the treatment, information on their termination was inaccessible. Of the remaining 240 patients, 222 (92.5%) recovered, while 15 (6.3%) had sequel and 4 (1.2%) had a relapse.

Table 6. Relationship between ESR and CRP values and clinical tables.

Properties*	Yes No	Count**	ESR average ± standard deviation	P-value
Spondylitis	Yes	70	42.1 ± 28.6	0.001
	No	231	29.6 ± 22.9	
Visceral abscess	Yes	15	44.9 ± 27.8	0.049
	No	286	31.9 ± 24.6	
Hepatomegaly	Yes	46	40.9 ± 25.9	0.012
	No	255	31.0 ± 24.4	
Fever	Yes	214	35.4 ± 25.8	0.001
	No	87	25.6 ± 21	
Sacroiliitis	Yes	83	38.3 ± 28	0.013
	No	218	30.3 ± 23.3	
Properties*	Yes No	Count	CRP average ± standard deviation	P-value
Neurobrucellosis	Yes	11	10.3 ± 9.8	0.000
	No	150	35.4 ± 42.8	
Spondylitis	Yes	67	43.9 ± 43.9	0.009
	No	94	26.4 ± 39.1	

*Only statistically significant properties are included.
**The number of evaluated patients is the number of patients whose ESR and CRP values were reviewed.

Table 7. Drug combinations used in patients.

Drug combination	Frequency (%)
Doxycycline + rifampicin	245 (77)
Doxycycline + rifampicin + streptomycin or gentamicin	28 (9)
Doxycycline + rifampicin + trimethoprim-sulfamethoxazole	15 (5)
Rifampicin + ciprofloxacin or ofloxacin	13 (4)
Doxycycline + ciprofloxacin	5 (1.5)
Doxycycline + ciprofloxacin or ofloxacin + streptomycin or gentamicin	3 (1)
Doxycycline + rifampicin + ciprofloxacin or ofloxacin	3 (1)
Doxycycline + streptomycin or gentamicin	3 (1)
Doxycycline + rifampicin	2 (0.5)
Total	317 (100)

Discussion

Brucellosis is the most common zoonotic disease in the world, and its seropositivity is very high, particularly in the eastern part of Turkey (4,5). The disease is common among the young and middle-aged populations in the countries in which it is endemic (1,6). This study demonstrates that the ages of the patients are compatible with the prolific

period. In only 11% of the cases were the patients 65 years old and above, which indicates that the disease may adversely affect the labor force. Furthermore, considering the future socioeconomic losses due to the disease, the importance of the disease is once more emphasized.

The disease was divided into acute, subacute, and chronic forms according to the initial symptomatic period. Different studies have observed the acute form in 25%-77% of the patients, the subacute form in 12.5%-59%, and the chronic form in 5%-27.5% (7-14). Such differences are considered to be associated with the cultural and socioeconomic status of the patient as well as with the differences in diagnostic approaches. However, it is obvious that the acute form is more frequent, that the symptoms of this period are more remarkable in distinguishing diagnosis, and that it allows for early diagnosis. Our study has identified fewer chronic forms than the other studies. This may be due to the fact that the disease is better considered by physicians and the patients in regions where it is endemic, as well as the chance of early diagnosis.

The results of this study have not identified any difference that is statistically significant between the phase of the disease and arthritis, arthralgia, splenomegaly, hepatomegaly, and weight loss; however, fever was found to be more common at a statistically significant level in the acute disease as compared to the other forms. Hepatomegaly and splenomegaly were not identified in patients in the chronic form. When the relationship between the course of the disease and its clinical forms was evaluated, there was no relationship between sacroiliitic and neurological involvement and the forms; however, spondylitis and visceral abscesses were found to be different at a statistically significant level across clinical forms. Spondylitis was rare in the acute form, and it was observed more frequently in the other forms. Visceral abscesses were observed particularly in subacute cases, whereas epididymo-orchitis was diagnosed in the acute and subacute forms rather than in the chronic form.

Typical brucellosis cases are presented with symptoms such as fever, chill, and fatigue. In a study with a vast patient population in Turkey, fever was identified in 76.9% of the acute cases, in 65.7% of the subacute cases, and in 57.6% of the chronic cases (15). The same study demonstrated that hepatomegaly and splenomegaly were less common in chronic cases as compared to acute and subacute cases, whereas spondylitis accompanied the chronic form, and orchitis never accompanied the chronic form (15).

Osteoarticular involvement was observed in 20%-85% of brucellosis cases (1,6). The difference of prevalence across studies may be associated with the fact that such complications are particularly suspected and examined. Our analysis identified peripheral arthritis in 4% of the patients, spondylitis in 22.7%, and sacroiliitis in 27.1%. There was no statistically significant difference in the concurrence of spondylitis and sacroiliitis, which are the most common osteoarticular involvements in brucellosis. As can be seen in our study, the lumbar vertebrae are the most frequently involved region, followed by the thoracal and cervical vertebrae. These are similar to the rates reported in the literature. Spondylitis is reported at varying rates, like 6%-58%, in the literature (16-18). Furthermore, as can be seen from our cases, the presence of paravertebral and/or epidural abscesses is a concern in the case of spondylitis. Spondylitis is reported to be more common in elderly males and chronic cases (19,20). This study has not identified any difference between sex and development of spondylitis, whereas advanced age was associated with the development of spondylitis.

Neurobrucellosis is identified in less than 5% of cases, and it is usually present with meningitis and meningoencephalitis (2,3). It was observed at 3.8% in our series. Isolation of bacteria is frequently impossible, and positive identification in the CSF in serological tests and demonstration of nucleic acid by polymerase chain reaction may help the diagnosis. The incidence of the disease is compatible with the literature (2,3).

Urogenital involvement is observed in 2%-10% of male patients with brucellosis. It is more common in acute and subacute cases, and it relapses in 5%-40% of the patients despite treatment (1,6). In our cases, its frequency in the acute and subacute phases was found to be about 7%. There was no information on termination of the epididymo-orchitis case, and there was a relapse in 1 of 8 cases.

Leukocytosis is rare in brucellosis, but it provides other reasons why brucellosis should be studied if there is not any focal reason. Still, one of the focal involvement findings is a remarkably high ESR. Colmenero et al. observed higher ESRs in complicated cases. In our study, there was a relationship between both high ESR and CRP and the presence of spondylitis. Similarly, demonstration of a significantly high rate of ESR and/or CRP in some complicated cases in this study indicates that these parameters can be helpful in diagnosis of complicated cases.

In this study, different treatment regimes were applied to the patients. Nonstandardization of treatment regimes and durations was remarkable. However, this was usual due to the application of individual treatments and different clinical presentations of the disease. The most commonly used treatment regime (77%) was doxycycline and rifampicin, which is recommended by the World Health Organization as the standard treatment.

The most significant shortcomings of the study were the 6-month follow-up period and the lack of information on termination of the disease, as most of the patients were not recorded after that period. As this may lead to biases in the determination of the actual ratio of relapses and failures and analysis of conditions that may affect termination, no comments were made on this issue.

Conclusion

This study has not provided any different information on age and sex selection in the incidence of brucellosis. Its clinical findings and incidences are compatible with the literature. Osteoarticular involvement and particularly the presence of spondylitis should be studied, and elderly patients should be meticulously scanned for complications. Laboratory parameters, patient's age, and duration of symptoms may help to identify complicated cases. In countries where the disease is endemic, its consideration as one of the first possibilities in the etiology of fever may lead to early diagnosis; however, failure to impose proper veterinary practices and prevent consumption of dangerous products by legal means will result in failure to prevent the disease.

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