Turkish Journal of Medical Sciences

Volume 43 | Number 2 Article 1

1-1-2013

Analysis of 161 adult patients with brucellosis

BİRCAN KAYAASLAN

ESRAGÜL AKINCI

ALİYE BAŞTUĞ

SELİM SIRRI EREN

PINAR ÖNGÜRÜ

See next page for additional authors

Follow this and additional works at: https://journals.tubitak.gov.tr/medical

 Part of the Medical Sciences Commons

Recommended Citation

KAYAASLAN, BİRCAN; AKINCI, ESRAGÜL; BAŞTUĞ, ALİYE; EREN, SELİM SIRRI; ÖNGÜRÜ, PINAR; BUT, AYŞE; YETKİN, MELTEM ARZU; and BODUR, HURREM (2013) "Analysis of 161 adult patients with brucellosis," *Turkish Journal of Medical Sciences*: Vol. 43: No. 2, Article 1. https://doi.org/10.3906/sag-1205-102

Available at: https://journals.tubitak.gov.tr/medical/vol43/iss2/1

This Article is brought to you for free and open access by TÜBİTAK Academic Journals. It has been accepted for inclusion in Turkish Journal of Medical Sciences by an authorized editor of TÜBİTAK Academic Journals. For more information, please contact academic.publications@tubitak.gov.tr.

Analysis of 161 adult patients with brucellosis

Authors
BİRCAN KAYAASLAN, ESRAGÜL AKINCI, ALİYE BAŞTUĞ, SELİM SIRRI EREN, PINAR ÖNGÜRÜ, AYŞE BUT, MELTEM ARZU YETKİN, and HURREM BODUR

This article is available in Turkish Journal of Medical Sciences: https://journals.tubitak.gov.tr/medical/vol43/iss2/1

TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2013) 43: 187-193
© TÜBİTAK
doi:10.3906/sag-1205-102

Analysis of 161 adult patients with brucellosis

Bircan KAYAASLAN*, Esragül AKINCI, Aliye BAŞTUĞ, Selim Sırrı EREN, Pınar ÖNGÜRÜ, Ayşe BUT, Meltem Arzu YETKİN, Hürrem BODUR

Department of Infectious Diseases and Clinical Microbiology, Ankara Numune Education and Research Hospital, Ankara, Turkey

Received: 25.05.2012 • **Accepted:** 13.07.2012 • **Published Online:** 15.03.2013 • **Printed:** 15.04.2013

Aim: To evaluate the epidemiology, clinical features, and complications of brucellosis.

Materials and methods: Between January 2005 and December 2008, 161 patients with brucellosis who were admitted to our clinic were evaluated prospectively.

Results: Of the patients, 97 (60.2%) were male, and the mean age was 47 ± 17 years (range: 16–79). There were 99 patients (61.5%) classified as acute, 36 (22.4%) classified as subacute, and 6 (3.7%) classified as having a chronic infection. Relapse or reinfection was observed in 20 (12.4%) patients. Blood culture positivity rates were 60.7% and 44.8% among acute and subacute cases, respectively (P = 0.008). In 40 of 70 culture positive patients, standard *Brucella* tube agglutination titers were found above 1/1280 (P = 0.03). Blood culture positivity was also higher in febrile patients (P = 0.001). Complications were detected in 66 of 161 patients (41.0%). Osteoarticular system involvement was the most common complication (50 patients, 31.1%). Fever, positive blood cultures, and hepatosplenomegaly were significantly higher in the group without complications (P < 0.05). Complications were significantly lower in acute infections than in subacute infections (P < 0.05). There were also higher complication rates detected in the patients with reinfection and relapse (P < 0.05).

Conclusion: In endemic regions, brucellosis is an important infectious disease causing chronic infections and complications.

Key words: Brucellosis, complication, relapse, reinfection

1. Introduction

Brucellosis is a serious public health problem in Turkey (1,2). Inadequate control programs and uncontrolled animal transportation increase the spread of brucellosis in some regions (3–5). Human brucellosis is a multisystem disease that may present a broad spectrum of clinical manifestations (6,7). The wide spectrum of clinical involvement and the nonspecific signs and symptoms interfere with the diagnosis of many other infectious diseases (8–10). In this study, we aimed to evaluate the epidemiology, clinical features, and complications of brucellosis.

2. Materials and methods

2.1. Patients

This study was conducted between January 2005 and December 2008 at the Infectious Diseases and Clinical Microbiology Department of Ankara Numune Education and Research Hospital. The study included 161 patients with brucellosis who were followed-up with prospectively.

2.2. Diagnosis and collection of data

The diagnosis was established by positive standard *Brucella* tube agglutination (STA) test (titer ≥ 1/160) and/or by isolation of *Brucella* species from blood or other body fluids in patients with signs and symptoms compatible with brucellosis.

Demographic, epidemiological, clinical, and laboratory data were collected from all patients according to the study protocol. Before starting therapy, 3 blood cultures were drawn regardless of fever. Radiological methods were used for the detection of complications. Cerebrospinal fluid was examined in patients with signs compatible with neurobrucellosis.

2.3. Classification and outcome

Based on the duration of the symptoms before admission to the hospital, patients were classified as having acute (<2 months), subacute (2–12 months), or chronic (>12 months) brucellosis. The disappearance of clinical symptoms and the return of abnormal laboratory test results to normal levels were accepted as recovery. In patients who completed the treatment with improvement, recurrence of clinical symptoms was accepted as relapse or reinfection.

2.4. Treatment

The patients without complications were treated with standard combination therapy, which consisted of

* Correspondence: drbican@gmail.com

doxycycline (200 mg/day) plus rifampicin (600 mg/day) for 6 weeks. In patients with osteoarticular involvement, initially a 3-drug regiment (doxycycline at 200 mg/day, rifampicin at 600 mg/day, and streptomycin at 1 g/day) was applied for 3 weeks and then the therapy was completed in 4–6 months with 2 drugs (doxycycline at 200 mg/day plus rifampicin at 600 mg/day). Intravenous ceftriaxone (4 g/day for 2–3 weeks) was added to doxycycline (200 mg/day) and rifampicin (600 mg/day) therapy for the patients diagnosed with neurobrucellosis. Drug combinations were modified according to the characteristics of the patients, their response to the therapy, and the side effects of the drugs.

2.5. Statistical analysis

Data were analyzed using SPSS 16.0. The Kolmogorov–Smirnov test, Pearson chi-square test, Student t-test, Fisher exact test and Mann–Whitney U test were used for univariate analysis, and backwards logistic regression analysis was used for multivariate analysis. $P < 0.05$ was considered statistically significant.

3. Results

There were 161 patients included in the analyses. Of these, 97 (60.2%) were male and the mean age was 47 ± 17 (range: 16–79) years old. Of the patients, 115 (71.4%) were animal handlers and 128 (79.5%) were consumers of unpasteurized dairy products. According to the duration of symptoms, 99 patients (61.5%) were classified as acute, 36 (22.4%) were classified as subacute, and 6 (3.7%) were classified as having chronic infection. Relapse or reinfection was observed in 20 (12.4%) patients who had been treated before. Reportedly, they had used the drugs irregularly or continued to consume unpasteurized dairy products.

On admission, the complaints were fever (77.7%), sweating (57.8%), malaise (56.5%), lumbar pain (45.3%), anorexia (41.6%), arthralgia (39.1%), myalgia (28%), headache (26.1%), weight loss (25.5%), nausea and vomiting (18%), neurological disorders (8.1%), and testicular pain (5.2%). Physical examination revealed high body temperature (>37.4 °C) (60.2%), limitations in joint movements (41.6%), hepatomegaly (11.2%), signs of arthritis (6.2%), neurological disorders (5.5%), orchitis (7.2%), splenomegaly (4.4%), lymphadenopathy (1.9%), and maculopapular rash (1.9%).

STA testing was positive for 157 patients (97.5%). In the analysis of blood samples, 98 patients (60.8%) had anemia (hemoglobin of <12.3 g/dL for females, <14.0 g/dL for males), 30 (18.6%) had leukopenia (<4000/mm^3), 6 (3.7%) had leucocytosis (>11,300/mm^3), and 24 (14.9%) had thrombocytopenia (<150,000/mm^3) (Table 1). Elevation of c-reactive protein (CRP) (>5 mg/dL) and erythrocyte sedimentation rate (ESR) (>20 mm/h) were detected in 134 (83.2%) and 100 patients (62.1%), respectively.

Table 1. Results of laboratory tests.

Laboratory tests		n	%
Hemoglobin (g/dL)			
	<14 for males, <12 for females	98	60.8
White blood cell count (/mm^3)			
	<4400	30	18.6
	4400–11,300	125	77.7
	>11,300	6	3.7
Thrombocyte count (/mm^3)			
	<150,000	24	14.9
	150,000–450,000	129	80.1
	>450,000	8	4.9
Aspartate aminotransferase/alanine aminotransferase ratio (>50 IU)		61	37.6
Sedimentation (>20 mm/h)		100	62.1
CRP (>5 mg/dL)		134	83.2
STA (>1/160)		157	97.6

Of the 135 patients whose blood cultures were drawn, *Brucella* spp. were grown in 70 cultures (51.9%). Blood culture positivity rates were 60.7% and 44.8% in acute and subacute patients, respectively. The difference was statistically significant (P = 0.008). No positive blood culture was detected in chronic patients. STA tests were positive in all blood culture-positive patients. A significant correlation was also detected between positive blood cultures and STA titers, which were significantly higher in culture-positive patients (P = 0.03). In 40 of 70 culture positive patients (57%), STA titers were found above 1/1280. The rate of blood culture positivity was also higher in febrile patients than afebrile patients (P = 0.001). From 70 blood culture-positive patients, 54 were febrile (77%).

Complications were detected in 66 of 161 patients (41.0%) and were significantly lower in acute infections than subacute infections (P < 0.05). The detected complication rates were also higher in the patients with reinfection and relapse (P < 0.05). Osteoarticular system involvement was the most common complication (50 patients, 31.1%). Other complications were neurobrucellosis (8 patients, 4.9%), orchitis (7 patients, 4%), and hepatitis (1 patient, 0.6%) (Table 2). Spondylitis was the most frequent osteoarticular involvement and was detected in 37 patients (74.0%). In the majority of cases, the lumbar spine was affected (17 cases, 44.7%). Paravertebral abscess was accompanied in 13 patients with spondylitis (35.1%). Other osteoarticular involvements were sacroiliitis (10 patients, 20%) and peripheral arthritis (8 patients, 16%). There were 4 patients with neurobrucellosis who had cranial nerve (C3, C7, C8) involvement. CSF examination results were abnormal (pleocytosis, high protein level, low glucose) and CSF *Brucella* tube agglutination tests were positive (between 1:32 and 1:512) for all of them. In 2 patients, *Brucella* spp. were grown in CSF cultures.

Table 2. Distribution of complications.

Complications	Patients	
	n	%
Osteoarticular involvement	50	31.1
Neurobrucellosis	8	4.9
Orchitis*	7	4.1
Hepatitis	1	0.6
Total	66	40.9

*Evaluated for male patients (n = 97).

The patients with and without complications were compared statistically and no significant differences were detected between the 2 groups for age, sex, presence of anemia, leukopenia and thrombocytopenia, or levels of ESR, CRP, and STA (P > 0.05). However, fever, positive blood cultures, and hepatosplenomegaly were significantly higher in the group without complications (P < 0.05) (Table 3).

Table 3. Comparison of noncomplicated and complicated cases.

Properties	Patients Noncomplicated		Complicated		P-value
	n	%	n	%	
Male	60	61.9	37	38.1	0.365
Female	35	54.7	29	45.3	
Age, years (range)	47	(16–79)	51	(18–75)	0.211
Acute	68	68.7	31	31.3	**0.002**
Subacute	16	44.4	20	55.6	**0.044**
Relapse/reinfection	7	35.0	13	65	**0.020**
Fever	80	65.0	43	35.0	**0.008**
Hepatosplenomegaly	16	80.0	4	20.0	**0.041**
Anemia	58	59.2	40	40.8	0.954
Leukopenia	23	74.2	8	25.8	0.056
Thrombocytopenia	18	75.0	6	25.0	0.084
Blood culture positivity	50	71.4	20	28.6	**<0.001**
Sedimentation (range)	34	(2–103)	39	(3–300)	0.631
CRP (range)	32	(2–192)	28	(0.9–413)	0.558
STA (range)	1280	(40–10,240)	640	(0–10,240)	0.412

Most of the patients (109, 67.7%) were treated with a combination of doxycycline and rifampicin. There were 37 patients (23%) given a combination of rifampicin and doxycycline plus streptomycin, and 8 patients (5.0%) were treated with a combination of rifampicin and doxycycline plus ceftriaxone (Table 4). Few patients came for follow-up visits after discontinuation of the antibiotic therapy, and no relapse or recurrence was detected.

4. Discussion

Osteoarticular infection is the most frequent complication of brucellosis and its prevalence varies between 10% to 80% in several studies (2,11–15). In a study reported by Bodur et al., brucellar spondylitis was diagnosed in 26 of 86 patients (30%) (16). In the present study, osteoarticular involvement was detected in 31.1% of the patients as the most frequent complication, and the spine was the most affected site (74%). However, these data varied in different studies. While Aygen et al. found that peripheral arthritis was the most involved area (47.2%), in the study reported by Kadanali et al., sacroiliitis was the body region most infected by brucellosis (72.2%) (12,17). On the other hand, in the study by Colmenero et al., it was suggested that spondylitis was the most commonly affected osteoarticular site with a rate of 47.4% (11). In our study, similar to the study of Colmenero et al., spondylitis was the most common osteoarticular infection of brucellosis. In another study from Turkey, a total of 1028 brucellosis patients were retrospectively analyzed. The most frequent symptoms were arthralgia (73.7%) and fever (72.2%), while the most common clinical findings were fever (28.8%) and hepatomegaly (20.6%). Focal involvement was found in 371 (36.1%) patients. The most frequent involvement was osteoarticular involvement with 260 patients (25.3%). The overall relapse rate was 4.7% and the highest rate (8.5%) was observed in patients with osteoarticular infection. Antibiotic regimens including doxycycline and streptomycin, with or without rifampin, were more effective than others in osteoarticular infection (18).

Spondylitis develops mainly in elderly males and in those with a chronic disease. It occurs most frequently in the lumbar region, followed by cervical and thoracic locations (2,11,13,16). In the course of brucellar spondylitis, paravertebral, epidural, and psoas abscess formation can occur in varying prevalences (2,13,19,20). In the present study, the lumbar spine was the most involved vertebral region, and paravertebral abscesses were detected in 13 patients with spondylitis (35.1%).

Sacroiliitis is one of the most often reported osteoarticular infections and is generally present with spondylitis (2). Kadanali et al. and Taşova et al. reported that sacroiliitis was the most common osteoarticular involvement in brucellosis (17,21). While spondylitis is seen in elderly males, sacroiliitis affects younger people of both sexes. It is generally unilateral (2,13,22,23). In our study, sacroiliitis was detected in 10 (20%) patients. Of these cases, 6 were unilateral and there were 4 with spondylitis. Peripheral arthritis is seen usually in younger people during acute infection (1,22). It is commonly presented as monoarthritis and rarely as oligoarthritis. Knee and hip joints are the most commonly involved joints (2,21,24,25). It is usually due to bacterial invasion of the synovial structure and sometimes can be reactive (26). Of our patients, 8 (16.0%) had peripheral arthritis, and in 5 of these cases the knee was affected. All patients experienced monoarticular involvement except for one.

In patients with spondylitis, duration of antibiotic therapy must be longer than in those without spondylitis (6,16). It was shown that the combination of doxycycline plus streptomycin is more efficient than the combination of doxycycline plus rifampicin. In the presence of

Table 4. Antimicrobial regiments and duration of the treatment.

Antimicrobial regiments	n	%	Duration
Rifampicin + doxycycline	109	67.7	6–8 weeks
*Doxycycline + streptomycin + rifampicin	37	23	4–6 months
**Rifampicin + doxycycline + ceftriaxone	8	5	2–10 months
Rifampicin + ciprofloxacin	2	1.2	4–6 months
Rifampicin + doxycycline + ciprofloxacin	2	1.2	3–6 months
Rifampicin + doxycycline + trimethoprim–sulfamethoxazole	2	1.2	3–6 months
Rifampicin + doxycycline + ofloxacin	1	0.7	6 months

*Streptomycin was given for the first 3 weeks. In 5 patients with spondylitis, antimicrobial therapy was extended to 9–10 months.
**Ceftriaxone was given for the first 4 weeks.

paravertebral abscess, surgical treatment may also be needed (12,27,28). In this study, patients with osteoarticular complications received a combination of doxycycline, rifampicin, and streptomycin for the first 3 weeks and thereafter the therapy was completed in 4–6 months with a doxycycline–rifampicin combination. In 5 patients with spondylitis, the antimicrobial therapy was extended to 9–10 months because of delayed clinical and radiological response. There were 2 patients with paravertebral abscesses who underwent surgical drainage in addition to antibiotic treatment. None of these patients experienced recurrence.

Epididymo-orchitis is another manifestation of brucellosis and is seen in 2%–20% of male patients. It is seen generally in the course of acute disease and in younger patients. The involvement is usually unilateral (2,7,29). In our study, epididymo-orchitis was detected in 7 of 97 male patients and 6 of these had unilateral involvement. A combination of doxycycline and rifampicin was given to the patients for 6–8 weeks. In the follow-up examinations, there was no recurrence.

Central nervous system involvement is an uncommon complication of brucellosis reported in less than 5% of patients in the literature, and it usually presents as acute or chronic meningitides (2). While Bodur et al. detected neurobrucellosis in 17.8% of patients, Yetkin et al. reported this rate as 6.6% (30,31). The reason for the rate differences may be associated with the different natures of the patient populations referred to the hospitals and the different times of the studies. The prevalence and nature of the disease may vary with time. Neurobrucellosis has no typical clinical picture or specific CSF findings. Imaging findings of neurobrucellosis are divided into 4 categories, namely normal, inflammation, white matter changes, and vascular changes (32). Meningeal signs are also detected in fewer than 50% of the patients. Thus, in brucellosis patients with any neurological symptoms, CSF samples must be obtained (30,31). Cranial nerve involvement is rarely seen in brucellosis and optic, oculomotor, abducens, facial, and vestibulocochlear nerves are most commonly involved (30,31,33).

The optimal antimicrobial regimen and appropriate duration of treatment of neurobrucellosis have not been determined yet. They must be individualized. Combination therapy with 2 or 3 antibiotics that penetrate the blood–brain barrier is recommended for at least 2 months (2,6,30). Bouza et al. recommended continuation of treatment until patients recover and the CSF glucose level returns to normal (33). The response to the treatment is usually favorable in most patients. However, patients with severe neurologic sequelae have been reported (2,30). In our study, the patients with neurobrucellosis were treated with a combination of doxycycline, rifampicin, and ceftriaxone for the first 4 weeks and the therapy was completed in 2–10 months with doxycycline and rifampicin. Except for one patient who died, all patients were cured without sequelae.

Antimicrobial susceptibility tests were not performed for the isolated strains because of the high risk of contagiousness among the laboratory staff and the tests' low value for prediction of clinical efficacy. In general, treatment failure is related to poor compliance of patients and inappropriate antibiotic therapy rather than antimicrobial resistance. Moreover, reports from Turkey indicate that drug resistance is not a problem in this country (34–36).

In general, the choice and duration of antimicrobial regimen should be based on presence of focal disease or underlying conditions. Most patients with acute brucellosis respond well to the combination of doxycycline plus aminoglycosides or rifampicin for 6 weeks. A combination of doxycycline with trimethoprim–sulfamethoxazole, or a quinolone plus rifampicin, are alternative treatment choices. The duration of antimicrobial therapy may be longer in patients with complications like spondylitis or endocarditis (37). Research for simple, low-cost, and effective treatment alternatives is in progress. In a recent metaanalysis, it was suggested that the most effective regimen was a combination of doxycycline for 45 days with streptomycin for 14 days, or gentamycin for 7 days, in noncomplicated brucellosis. The alternative was a combination of doxycycline and rifampicin. Triple therapy with doxycycline–rifampicin–aminoglycoside was not recommended as the best regimen (38).

In brucellosis, the diagnosis is confirmed with the isolation of *Brucella* spp. from blood, bone marrow, or other tissues (2). Since culture techniques are lengthy, risky processes that have low sensitivity, the diagnosis of brucellosis is mostly based on high titers of specific antibodies. The SAT is accepted as the reference method in the serological diagnosis of human brucellosis. SAT titers of ≥1:160 are consistent with active brucellosis when accompanied by a compatible clinical course and epidemiological history (39). In the present study, a correlation was found between the presence of fever and high STA titers, and a correlation was also detected between blood culture positivity and acute disease. These results are similar to the results of previous studies reported by Gotuzzo et al. and Özkurt et al. (40,41). This is probably due to the high risk of bacteremia during acute infection. However, the bacteria can be found in blood cultures of afebrile patients. Therefore, blood cultures should be drawn also in patients without fever. Although the isolation of the bacteria from blood cultures is very important for the diagnosis of chronic infections, we found no culture positivity in chronic cases. This may be due to several factors, such as the low level of bacteremia

and previous antibiotic usage. In a comparison of the cases with and without complications, it was found that rates of positive blood cultures, fever, and hepatosplenomegaly were higher in noncomplicated cases. Considering that positive blood cultures and fever are most common in acute cases, this result indicates that complications develop more frequently in subacute and chronic phases of the disease than in the acute phase. It was shown that a delay of more than 14 days in the diagnosis of brucellosis significantly increased the risk of complications (P = 0.002). In addition, long-term follow-up exams indicated that 64% of the patients developed recurrent symptoms (42).

In conclusion, human brucellosis is a multisystem disease and presents with a broad spectrum of clinical manifestations. Although brucellosis is endemic in Turkey, it often remains undiagnosed. Thus, healthcare workers should always keep acute and chronic brucellosis in mind, especially in differential diagnosis of infectious diseases including osteoarticular, neurologic, hematologic, and genitourinary disorders. Delayed diagnosis or inadequate therapy may cause the development of chronic infections and complications. A high cure rate can be achieved with appropriate antibiotic combinations with an adequate duration. Early and successful treatment is thus effective to prevent the complications of brucellosis.

References

1. Koneman EW. *Brucella* species. In: Koneman EW, Allen DS, Janda WM, Shreckenberger PC, Winn WC, editors. Color atlas and textbook of diagnostic microbiology. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 1997. p.431–6.
2. Young EJ. *Brucella* species. In: Mandell GL, Bennet JE, Dolin R, editors. Principles and practice of infectious diseases. Philadelphia: Churchill Livingstone; 2005. p.2669–74.
3. Atmaca S, Özekinci T, Akpolat N, Elçi S, Suay A, Arıkan E. Brucellosis seroprevalence in Southeast Turkey (Diyarbakır). Turk J Med Sci 2004; 34: 251–5.
4. Gwida M, Al Dahouk S, Melzer F, Rösler U, Neubauer H, Tomaso H. Brucellosis- regionally emerging zoonotic disease? Croat Med J 2010; 51: 289–95.
5. Yumuk Z, O'Callaghan D. Brucellosis in Turkey - an overview. Int J Infect Dis 2012; 16: 228–35.
6. Solera J, Martinez-Alfaro E, Espinosa A. Recognition and optimum treatment of brucellosis. Drugs 1997; 53: 245–56.
7. Doğanay M, Meşe EA. Topçu AW, Söyletir G, Doğanay M, eds. İnfeksiyon hastalıkları ve mikrobiyolojisi. Ankara: Nobel Tıp Kitapevleri; 2008. p.897–909 (in Turkish).
8. Akdeniz H, Irmak H, Demiröz AP. Evaluation of brucellosis cases in Van region of Eastern Anatolia: a 3 year experience. Nogoya Med J 1998; 42: 101–10.
9. Taşova Y, Saltoğlu N, Yılmaz G, İnal S, Aksu HSZ. Bruselloz: 238 erişkin olgunun klinik, laboratuvar ve tedavi özelliklerinin değerlendirilmesi. Turkish J Infect 1998; 12: 307–12 (in Turkish).
10. Kadanali A, Ozden K, Altoparlak U, Erturk A, Parlak M. Bacteremic and nonbacteremic brucellosis: clinical and laboratory observations. Infection 2009; 37: 67–9.
11. Colmenero JD, Reguera JM, Mortos F, Sanchez-De-Mora D, Delgado M, Causse M et al. Complications associated with *Brucella melitensis* infection: a study of 530 cases. Medicine (Baltimore) 1996; 75: 195–211.
12. Aygen B, Sümerken B, Kardaş Y, Doğanay M, İnan M. Bruselloz: 183 olgunun değerlendirilmesi. KLİMİK Derg 1995; 8: 13–6 (in Turkish).
13. Solera J, Lozano E, Martinez, Alfaro E, Espinosa A, Castillejos ML et al. Brucellar spondylitis: review of 35 cases and literature survey. Clin Infect Dis 1999; 29: 1440–9.
14. Çalık Ş, Gökengin AD. Human brucellosis in Turkey: a review of the literature between 1990 and 2009. Turk J Med Sci 2011; 41: 549–55.
15. Bulut C, Yetkin MA, Yılmaz G, Erdinç FŞ, Hatipoğlu ÇA, Kınıklı S et al. Assessment of the findings on the existence of complications in brucellosis. Turk J Med Sci 2011; 41: 275–82.
16. Bodur H, Erbay A, Colpan A, Akinci E. Brucellar spondylitis. Rheumatol Int 2004; 24: 221–6.
17. Kadanali A, Varoglu E, Kerek M, Tasyaran MA. Tc-99m polyclonal human immunoglobulin scintigraphy in brucellosis. Clin Microbiol Infect 2005; 11: 480–5.
18. Buzgan T, Karahocagil MK, Irmak H, Baran AI, Karsen H, Evirgen O et al. Clinical manifestations and complications in 1028 cases of brucellosis: a retrospective evaluation and review of the literature. Int J Infect Dis 2010; 14: e469–78.
19. Aygen B, Eşel D, Erdoğan N, Sümerkan B, Doğanay M. Psoas abscess secondary to brucellar spondylitis. Turk J Med Sci 2002; 32: 81–3.
20. Kurtaran B, Candevir A, İnal AS, Kömür S, Akyıldız Ö, Saltoğlu N et al. Clinical appearance of brucellosis in adults: fourteen years of experience. Turk J Med Sci 2012; 42: 497–505.
21. Taşova Y, Saltoğlu N, Şahin G, Aksu HSZ. Osteoarticular involvement of brucellosis in Turkey. Clin Rheumatol 1999; 18: 214–9.
22. Gotuzzo E, Carillo C. *Brucella*. In: Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious diseases. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2004. p.1717–24.
23. Ariza J, Pujol M, Valverde J, Nolla JM, Rufí G, Viladrich PF et al. Brucellar sacroiliitis: findings in 63 episodes and current relevance. Clin Infect Dis 1993; 16: 761–5.

24. Hashemi SH, Keramat F, Ranjbar M, Mamani M, Farzam A, Jamal-Omidi S. Osteoarticular complications of brucellosis in Hamedan, an endemic area in the west of Iran. Int J Infect Dis 2007; 11: 496–500.

25. Khateeb MI, Araj GF, Majeed SA, Lulu AR. Brucella arthritis: a study of 96 cases in Kuwait. Ann Rheum Dis 1990; 49: 994–8.

26. Resnick D, Niwayama G. Osteomyelitis, septic arthritis, and soft tissue infection: organisms. In: Resnick D, editor. Diagnosis of bone and joint disorders. Philadelphia: WB Saunders Company; 1995. p.2448–558.

27. Montejo JM, Alberolo I, Glez-Zarete P, Alvarez A, Alonso J, Canovas A et al. Open randomized therapeutic trial of six antimicrobial regimens in the treatment of human brucellosis. Clin Infect Dis 1993; 16: 671–6.

28. Cisneros JM, Viciana P, Colmenero J, Pachon J, Martinez C, Alarcon A. Multicenter prospective study of treatment of *Brucella melitensis* brucellosis with doxycycline for 6 weeks plus streptomycin for 2 weeks. Antimicrob Agent Chemother 1990; 34: 881–3.

29. Akinci E, Bodur H, Cevik MA, Erbay A, Eren SS, Ziraman I et al. A complication of brucellosis: epididymoorchitis. Int J InfectDis 2006; 10: 171–7.

30. Bodur H, Erbay A, Akinci E, Çolpan A, Çevik MA, Balaban N. Neurobrucellosis in an endemic area of brucellosis. Scand J Infect Dis 2003; 35: 94–7.

31. Yetkin MA, Bulut C, Erdinc FS, Oral B, Tulek N. Evaluation of the clinical presentations in neurobrucellosis. Int J Infect Dis 2006; 10: 446–52.

32. Kizilkilic O, Calli C. Neurobrucellosis. Neuroimaging Clin N Am 2011; 21: 927–37.

33. Bouza E, García de la Torre M, Parras F, Guerrero A, Rodríguez-Créixems M, Gobernado J et al. Brucellar meningitis. Rev Infect Dis 1987; 9: 810–22.

34. Bodur H, Balaban N, Aksaray S, Yetener V, Akinci E, Colpan A et al. Biotypes and antimicrobial susceptibilities of *Brucella* isolates. Scand J Infect Dis 2003; 35: 337–8.

35. Ayaşlıoğlu E, Kılıç S, Aydın K, Kılıç D, Kaygusuz S, Ağalar C. Antimicrobial susceptibility of *Brucella melitensis* isolates from blood samples. Turk J Med Sci 2008; 38: 257–62.

36. Kaya O, Akçam FZ, Yaylı G. Investigation of the in vitro activities of various antibiotics against *Brucella melitensis* strains. Turk J Med Sci 2012; 42: 145–8.

37. Solera J. Update on brucellosis: therapeutic challenges. Int J Antimicrob Agents 2010; 36: S18–20.

38. del Pozo JSG, Solera J. Systematic review and meta-analysis of randomized clinical trials in the treatment of human brucellosis. PLoSOne 2012; 7: e32090.

39. Al Dahouk S, Nöckler K. Implications of laboratory diagnosis on brucellosis therapy. Expert Rev Anti Infect Ther 2011; 9: 833–45.

40. Gotuzzo E, Carrillo C, Guerra J, Llosa L. An evaluation of diagnostic methods for brucellosis-the value of bone marrow culture. J Infect Dis 1986; 153: 122–5.

41. Özkurt Z, Kaya A, Taşyaran MA, Yılmaz Ş. Bruselloz tanısında standart tüp aglütinasyon testi, kan ve kemik iliği kültürlerinin tanı değerlerinin karşılaştırılması. İnfeksiyon Dergisi 2000; 14: 463–8 (in Turkish).

42. Eales KM, Norton RE, Ketheesan N. Brucellosis in Northern Australia. Am J Trop Med Hyg 2010; 83: 876–8.