



Seroprevalence of Brucellosis in Human Immunodeficiency Virus Infected Patients in Hamadan, Iran

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Objectives: Brucellosis is a systemic disease with a wide spectrum of clinical manifestations. This study aimed to determine the seroprevalence of brucellosis in human immunodeficiency virus (HIV) infected patients in Hamadan Province in the west of Iran.

Methods: A total of 157 HIV-infected patients were screened through standard serological tests, including Wright's test, Coombs' Wright test, and 2-mercaptoethanol *Brucella* agglutination test (2ME test), blood cultures in Castaneda media, and CD4 counting. Data were analyzed using Stata version 11.

Results: Wright and Coombs' Wright tests were carried out, and only 5 (3.2%) patients had positive serological results. However, all patients had negative 2ME results, and blood cultures were negative for *Brucella* spp. Moreover, patients with positive serology and a mean CD4 count of 355.8 ± 203.11 cells/ μ L had no clinical manifestations of brucellosis, and, and the other patients had a mean CD4 count of 335.55 ± 261.71 cells/ μ L.

Conclusion: Results of this study showed that HIV infection is not a predisposing factor of acquiring brucellosis.

Key Words: brucellosis, human immunodeficiency virus, serology

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INTRODUCTION

Brucella is a gram-negative coccobacilli, and at least four species of *Brucella*, including *Brucella abortus*, *Brucella suis*, *Brucella melitensis*, and *Brucella canis*, are pathogenic to humans. *Brucella* is an intracellular bacterium that is phagocytosed by polymorphonuclear and mononuclear leukocytes, including macrophages essential for the eradication of the disease in humans. Phagocytosis and cellular immunity help in controlling brucellosis.

Human brucellosis is a zoonotic bacterial infection caused by these bacteria [1-4] through direct or indirect contact with infected animals or dairy products [5]. Brucellosis manifestations range from asymptomatic infection to acute, subacute, and chronic forms of the disease.

Brucellosis is an endemic disease in Iran most commonly caused by *B. melitensis*. In some provinces, the incidence of brucellosis is high, particularly in the Hamadan Province with an incidence rate of 31.7 per 100,000 people in 2008 [6] and 36.7 per 100,000 people in 2010 [7]. Moreover, a higher incidence rate of 62.9 and 81.4 per 100,000 people was observed in 2012



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and 2013, respectively. However, the incidence rate in the whole country was 21 per 100,000 people in 2012, and the incidence rate in Hamadan was nearly three times than that of the whole country [8]. In the endemic areas of Iran, a high percentage of these patients were asymptomatic, and fewer than 10% of them were diagnosed early [9,10].

The eradication of brucellosis depends on the host humoral and cell-mediated immunity. Therefore, theoretically, human immunodeficiency virus (HIV)-positive patients with disrupted cell-mediated immunity are susceptible to brucellosis, and the infection is common in endemic areas. Moreover, the symptoms of brucellosis are severe in patients with immune deficiency.

Acquired immunodeficiency syndrome (AIDS) is a disease caused by HIV. This disease is associated with severe cellular and humoral immunity deficiencies that weaken the host defense system, hence, resulting in susceptibility to opportunistic infections. Some diseases are common in HIV-positive patients, such as pneumococcal pneumonia, pulmonary tuberculosis, toxoplasmosis infections, and fungal infections [11–13].

According to the Center for Disease Control and Prevention of United States (CDC), HIV-infection is classified into four stages. Patients with stage III AIDS have a CD4 count below 200 cells/ μ L or a positive CD4 lymphocyte percentage below 14% [14]. On March 20, 2013, a total of 652 patients were infected with HIV and AIDS in Hamadan, of which 52.8% of patients were 25 to 34 years and 86% and 14% were males and females, respectively; which, this HIV prevalence rate (36.2 per 100,000 people) was nearly like the country's incidence rate (36.5 per 100,000 people) in the same year [15].

The present study aimed to identify the seroprevalence of *Brucella* infection in HIV-positive patients in the Hamadan Province, an endemic area in Iran. Based on the diagnosis and treatment of HIV-positive patients with brucellosis, we can prevent the occurrence of the severe forms of the disease [16,17].

MATERIALS AND METHODS

An analytical cross-sectional study was performed. All HIV-positive patients who were referred for outpatient therapy at the Behavioral Diseases Counseling Center (BDCC) of the Shohada Clinic in the Hamadan Province were enrolled in the study. Each patient testing positive with enzyme-linked immunosorbent assay (ELISA) and Western blot from August 2012 to August 2013 was enrolled in the study. Written informed consents were obtained. All HIV-positive patients were referred by their physician for the treatment of the diseases to the BDCC in Hamadan, and were included in the study. Furthermore, we coordinated with

the city health centers for the participation of HIV-positive patients in the Hamadan Province. Patients wanting to participate in the study were referred to the BDCC in Hamadan, and clinical examinations were performed for each patient after obtaining the informed consent.

Demographic information, such as age, sex, antiretroviral therapy, and duration of the HIV infection, was obtained through a designed questionnaire, and 5 mL of blood was drawn from each patient for CD4 count by flow cytometry at the laboratory of BDCC in Hamadan. Moreover, 15 mL of blood sample was collected from each patient for serological tests, including Wright test, Coombs Wright test, and 2-mercaptoethanol *Brucella* agglutination test (2ME test), and blood cultures using Castaneda medium (Bahar Afshan Co., Tehran, Iran). Lastly, all the samples were sent to the Reference Laboratory in Hamadan. Blood cultures were held for 6 weeks using Castaneda medium to ensure the growth of *Brucella*. Wright, Coombs Wright, and 2ME kits (Pasteur Institute of Iran, Tehran, Iran) and Castaneda mediums were purchased.

Patients with a Wright titer equal to or greater than 1/80 or 2ME titer equal to or greater than 1.40 are considered to be infected with *Brucella*. Moreover, those with positive Coombs Wright and blood culture test results were also infected with the bacteria [3].

A person without clinical signs of brucellosis and without positive blood culture for *Brucella* and with positive Wright, Coombs Wright, or 2ME test results is considered to have sub-clinical brucellosis.

Of the 181 HIV-positive patients who have a record in the BDCC, 157 patients were enrolled in the study, and 24 patients were excluded due to the lack of consent. For the statistical analysis of noun data, chi-square test was carried out, and the *t*-test was performed for the analysis of quantitative data. All statistical analysis was carried out using Stata ver. 11 (Stata Co., College Station, TX, USA) with a 95% confidence interval.

RESULTS

Of the 181 HIV-positive patients, 24 patients were not included in the study due to lack of consent or cooperation during blood sampling. A total of 157 patients were enrolled in the study, including 117 (74.5%) male and 40 (25.4%) female aged 2 to 66 years with an average age of 36.17 ± 0.81 years. A total of 129 (82.2%) patients were living in the urban areas, and 28 (17.8%) patients were in the rural areas. Majority of patients that were involved in 115 (73.2%) cases were from Hamadan city, and 2 (1.3%) of these patients were from Bahar city (Table 1).

A total of 105 (66.9%) patients had AIDS, and 52 patients (33.1%) did not acquire AIDS.

Of the 157 patients, 154 (98.1%) had negative Wright serologic test results. However, two (1.3%) had a Wright titer of 1/20, and one (0.6%) had a Wright titer of 1.40.

All patients had negative 2ME test results. Of the 157 patients, 152 (96.8%) had negative Coombs test results, and two (1.3%) had a Coombs titer of 1/20. Overall, 5 people had positive serologic test results for brucellosis or subclinical infections. However, none of them showed symptoms of brucellosis (Table 2).

Of the five patients with positive serologic test results, four were men and one was a woman aged 28 to 56 years, with an average age of 35.8 ± 11.41 years. Blood cultures of the 157 patients were performed using Castaneda medium, and no *Brucella* growth was observed after 6 weeks. Of the 157 HIV-positive patients, five patients (3.2%) had a history of brucellosis. However, all these patients had negative Wright, Coombs Wright, and 2ME test results. A total of 152 patients (96.8%) did not have any history of brucellosis, of which five patients had positive Coombs test results with titers ranging from 1/20 to 1/40. Moreover, three

patients had a Wright titer between 1/20 and 1/40. As shown in Table 3, the relationship between the positive Wright serological test results and history of brucellosis was not significant ($p = 0.199$). In addition, no significant relationship was observed between the positive Coombs serological test results and history of brucellosis ($p = 0.951$).

None of the patients were clinically diagnosed with active brucellosis, and only five patients were seropositive with a low titer that can be divided into the subclinical forms of brucellosis. Of the five patients with a history of brucellosis, four (80.0%) had AIDS, and 1 (20.0%) did not acquire AIDS. Of the 152 patients with a negative history of brucellosis, 98 (64.5%) HIV-positive patients were in stage III, and 53 (34.9%) patients had AIDS. Out of the 157 patients, 105 were had AIDS, with an average CD4 cell count of 230.14 ± 157.65 cells/ μ L, ranging from 9 to 717 cells/ μ L. The rest of the patients with AIDS had a mean CD4 count of 562.16 ± 292.26 cells/ μ L, ranging from 218 to 1,439 cells/ μ L. The average CD4 count of the five patients with seropositive results for brucellosis was 355.8 ± 203.11 cells/ μ L, and 152 patients with negative serologic test results have an average CD4 count of 335.55 ± 261.71 cells/ μ L, which was not statistically significant ($p = 0.864$). Moreover, three patients with positive Wright test results had AIDS. However, the value was not statistically signifi-

Table 1. Distribution of HIV-positive patients based on different locations in Hamedan Province

Location	Patient
Hamadan	115 (73.2)
Malayer	10 (6.4)
Asadabad	8 (5.1)
Nahavand	8 (5.1)
Kaboodar ahang	6 (3.8)
Toyserkan	3 (1.9)
Razan	3 (1.9)
Famenin	2 (1.3)
Bahar	2 (1.3)

Values are presented as number (%).
HIV, human immunodeficiency virus.

Table 2. Distribution of seropositive results of Wright, Coombs Wright and 2ME tests in patients with HIV based on the AIDS staging system

Test	AIDS stage ^a	
	With AIDS (n = 105)	Without AIDS (n = 52)
Wright	3 (91.1)	154 (98.1)
Coombs Wright	5 (3.2)	152 (96.8)
2ME test	0 (0)	0 (0)

Values are presented as number (%).
2ME test, 2-mercaptoethanol *Brucella* agglutination test; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.
^aPatients who had signs or indications of AIDS or had a CD4 count below 200 were considered with AIDS, and those who had a CD4 count equal or greater than 200 were considered without AIDS [12].

Table 3. Distribution of HIV-positive patients with seropositive brucellosis according to the history of brucellosis infection

Test	History of brucellosis in patients with HIV				p-value
	Positive (n = 5)		Negative (n = 152)		
	Negative serology	Positive serology	Negative serology	Positive serology	
Wright	5	0	149	3	0.951
Coombs Wright	5	0	147	5	0.919
2ME test	5	0	152	0	-

HIV, human immunodeficiency virus; 2ME test, 2-mercaptoethanol *Brucella* agglutination test.

Table 4. Distribution of clinical symptoms in HIV-positive patients based on the AIDS staging system

Clinical sign	AIDS stage				<i>p</i> -value
	AIDS		Not AIDS		
	No	Yes	No	Yes	
General body pain	65 (61.9)	40 (38.1)	31 (59.6)	21 (38.5)	0.935
Headache	64 (61.0)	41 (39.0)	30 (57.7)	22 (42.3)	0.964
Back pain	76 (72.4)	29 (27.6)	35 (67.3)	17 (32.7)	0.827
Low back pain	65 (61.9)	40 (38.1)	29 (55.8)	23 (44.2)	0.692
Arthralgy	67 (63.8)	38 (36.2)	39 (75.0)	13 (25.0)	0.065
Testicular pain (men)	101 (96.2)	4 (3.8)	51 (98.1)	1 (1.9)	0.851
Abdominal pain	87 (82.9)	18 (17.1)	40 (76.9)	12 (23.1)	0.947
Sleep disorders	73 (69.5)	32 (30.5)	36 (69.2)	16 (30.8)	0.752
Fatigue	33 (31.4)	72 (68.6)	18 (34.6)	34 (65.4)	0.571
Constipation	80 (76.2)	25 (23.8)	40 (76.9)	12 (23.1)	0.596
Diarrhea	96 (91.4)	9 (8.6)	47 (90.4)	5 (9.6)	0.576
Cough	68 (64.8)	37 (35.2)	34 (65.4)	18 (34.6)	0.637
Chill	84 (80.0)	21 (20.0)	41 (78.8)	11 (21.2)	0.687
Sweating	55 (52.4)	50 (47.6)	22 (42.3)	30 (57.7)	0.329
Anorexia	63 (60.0)	42 (40.0)	31 (59.6)	21 (40.4)	0.760
Weight loss	55 (52.4)	50 (47.6)	31 (59.6)	21 (40.4)	0.345
Fever	97 (92.4)	8 (7.6)	46 (88.5)	6 (11.5)	0.887
Arthritis	101 (96.2)	4 (3.8)	48 (92.3)	4 (5.7)	0.564
Vertebral tenderness	95 (90.5)	10 (9.5)	45 (86.5)	7 (13.5)	0.927
Orchitis (men)	101 (96.2)	4 (3.8)	30 (57.7)	22 (42.3)	0.786
Lymphadenopathy	98 (93.3)	7 (6.7)	47 (90.4)	5 (9.6)	0.725
Splenomegaly	86 (81.9)	19 (18.1)	43 (82.7)	9 (17.3)	0.524
Jaundice	103 (98.1)	2 (1.9)	50 (96.2)	2 (3.8)	0.230
Beech	103 (98.1)	2 (1.9)	50 (96.2)	2 (3.8)	0.326
Hepatomegaly	93 (88.6)	12 (11.4)	47 (90.4)	5 (9.6)	0.285

Values are presented as number (%). The sum of the percentages does not equal 100% because of rounding. HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

cant ($p = 0.445$).

Of the five patients with positive Coombs test results, four patients had AIDS, and 1 patient did not acquire AIDS. However, the value was not statistically significant ($p = 0.584$). The duration of from diagnosis was from one month until 12 years with an average of 4.278 ± 3.114 years. Eighty (76.2%) out of 105 patients with AIDS were under antiretroviral treatment. Table 4 shows the clinical signs and symptoms of HIV-positive patients without AIDS, and no significant relationship was observed between the two groups.

The most common symptoms of this disease were fatigue

(66.2%), sweating (49.7%), weight loss (42.3%), anorexia (34.5%), headache (34.5%), back pain (34.5%), and body pain (38.2%). All these symptoms are also observed in patients with brucellosis. However, none of the patients had acute, subacute, or chronic brucellosis, and those with positive serologic test results and low titers did not show specific clinical symptoms or organ involvement to diagnose brucellosis. Table 5 shows the hematologic changes in HIV-positive patients with and without AIDS, and the relationship was not statistically significant ($p > 0.05$).

Table 5. Distribution of hematological changes in HIV-positive patients based on the AIDS staging system

Variable	AIDS stage		p-value
	Positive	Negative	
Leukopenia (< 4,000/mm ³)	34 (33.3)	3 (6.0)	0.001
Natural leukocyte counts (4,000–10,000/mm ³)	67 (65.7)	46 (92.0)	
Leukocytosis (> 10,000/mm ³)	1 (1.0)	1 (2.0)	
Hemoglobin anemia (< 14 g/dL in males, < 12 g/dL in females)	60 (58.3)	14 (28.0)	0.001
Thrombocytopenia (< 10,000/mm ³)	23 (22.3)	5 (10.0)	0.064

Values are presented as number (%).

HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

DISCUSSION

Brucellosis is a bacterial disease common in humans and animals. Humoral and cellular immunity is essential in controlling brucellosis. Therefore, humoral and cellular immunity deficiencies could influence its progression. AIDS is caused by the HIV and is associated with severe host cellular and humoral immunity deficiencies. It eventually predisposes patients to opportunistic infections. This study aimed to investigate the seroprevalence of brucellosis in HIV-infected patients in the Hamadan Province, west of Iran. On December 20, 2013, according to the national statistics, the estimated number of registered patients with AIDS and HIV was 27,416 (89% men and 11% women). Approximately 45% of the patients were aged between 25 to 34 years at the time of infection, and the incidence rate was about 36.5 per 100,000 people. In Hamadan Province, 651 patients with AIDS and HIV were registered until March 20, 2013, and 8.52% of patients were 25 to 34 years, of which 86% were men and 14% were women. The distribution of HIV-positive patients per 100,000 people was 2.36, which is the same as the prevalence rate in the country, a total of 228 patients died, and 423 individuals survived. Hamadan Province and Malayer city had 392 and 82 cases, respectively, with the highest number of HIV-infected patient compared to other cities in the province, and Famenin had 10 HIV-positive patients, with the lowest rate in the province. In our study, the distribution pattern and age of HIV-positive patients were similar to those of the national statistics.

Hajiabdolbaghi et al. [18] conducted a study between 2007 and 2008 in Imam Khomeini Hospital, Tehran, on 184 HIV-positive patients. In their study, 80.98% of patients were men and 19.02% were women with an average age of 37.6 years, of which 94% were residents in urban areas and 6% lived in rural areas.

Their age and sex parameters were almost similar to the present study. However, the locations were different. This result is possibly due to the higher ratio of rural population to urban population in Hamadan Province than Tehran. In addition, villagers have a difficulty in accessing Tehran, the capital city of Iran.

Of the 157 patients, five patients (3.2%) had serological Wright and Coombs titers ranging from 1/20 to 1/40. All 157 patients were tested negative for *Brucella* by blood culture using Castaneda medium. Moreover, all patients had negative 2ME test results. Brucellosis was not observed. However, subclinical brucellosis was present. Hajiabdolbaghi et al. [18] showed that 159 (86.4%) out of 184 patients had negative serologic test results for brucellosis, and 11 patients (6.0%) had positive serologic titers over 1/160, which is twice of our study result. In the present study conducted in Iran, an incidence rate of 3.0% and 1/0% was obtained for brucellosis and symptomatic brucellosis in Iran, respectively [18], which is roughly the same as that of the whole country. Thus, in HIV diseases, the infection risk of brucellosis was not high, unlike the results of Hajiabdolbaghi et al. [18].

In our study, five (3.2%) out of 157 HIV-positive infection had a history of brucellosis. However, all of them had negative Wright, Coombs Wright, and 2ME test results, and 5 (3.3%) out of 152 patients who hadn't a history of brucellosis, had serological Wright and Coombs test results with low positive titers, and the relationship was not statistically significant ($p = 0.199$). However, in the study conducted by Hajiabdolbaghi [18], two out of 11 patients with positive serologic tests had a history of brucellosis. In our study, 105 out of 157 patients with an average CD4 cell count of 230.14 ± 157.65 cells/ μ L had AIDS, and the rest of the patients with an average CD4 cell count of 562.16 ± 292.26 cells/ μ L did not have AIDS.

The average CD4 count in five patients with seropositive results for brucellosis was 355.8 ± 203.11 cells/ μ L, and in 152 patients with negative serologic test results, the average CD4 count was 335.55 ± 261.71 cells/ μ L, which was not statistically significant ($p = 0.864$). Three patients with positive Wright's test results had HIV. However, the value was not statistically significant ($p = 0.455$). Of the five patients with positive Coombs test results, four patients had AIDS, and 1 patient did not acquire AIDS. However, the result was not statistically significant as well ($p = 0.548$). In the study conducted by Hajiabdolbaghi et al. [18], the average CD4 count of all patients was 320.2 cells/ μ L, and 31% had a CD4 count below 200 cells/ μ L. In 11 patients with positive serologic test results, the average CD4 count was 235 cells/ μ L, which was less than the average value in our study. The duration of HIV infection from diagnosis was from 1 month to 12 years with an average of 4.278 ± 3.114 years, and 80 (76.2%) of 105 patients with AIDS were under antiretroviral treatment. However, in the

study conducted by Hajiabdolbaghi et al. [18], the average illness duration after diagnosis was 3.2 years. In addition, 117 (63.6%) patients were under antiretroviral treatment, which was lower than the value obtained in our study. This result is possibly due to the higher percentage of patients with AIDS and a CD4 count less than 200 cells/ μ L in the previous. The clinical signs and symptoms of patients with HIV infection include fatigue (66.2%), sweating (49.7%), weight loss (42.3%), anorexia (34.5%), headache (34.5%), back pain (34.5%), and general body pain (38.2%), and all of these symptoms can also be observed in patients with brucellosis [2,19,20]. However, none of the patients were infected with acute or subacute brucellosis, and people who had positive serologic test results and low titers did not have any clinical signs of acute infection. In our study, hematological changes, including leukopenia, thrombocytopenia, and anemia, in patients with late-stage HIV infection were significantly higher than in HIV-positive patients without AIDS ($p < 0.05$).

In a study conducted by Abdollahi et al. [21] that involved 90 HIV-positive patients and 100 controls in a university hospital in Tehran, the average age of participants was 36.5 years, and 75.6% were male. The percentage of HIV-positive patients who were seropositive for brucellosis were 73.3% (66 patients), and in the control group, 30% of patients were infected with brucellosis, which was statistically significant ($p < 0.001$).

In HIV-positive patients, the average CD4 count was about 297 cells/ μ L, and the white blood cell count of HIV-positive patients with brucellosis was significantly lower than that of patients without brucellosis. In a previous study, the prevalence of brucellosis in HIV-positive patients was more than twice than that of the control group and was higher than that of our study.

In another study by Moreno et al. [22] in Spain in 1998, 12 HIV-positive patients had brucellosis, of which eight cases were detected had a positive culture and four cases had positive serologic test results. Majority of the patients were men, and 11 patients with brucellosis did not have signs of HIV infection, and their mean CD4 count was 588 cells/ μ L. All 11 patients had symptoms, such as fever, arthralgia, myalgia, and sweating, and four patients had focal signs. After 18 months of treatment, two patients had relapse. In our study, no positive culture or positive serology and any clinical symptoms of brucellosis were observed. Five cases had seropositive results with low titer and a CD4 count higher than 350 cells/ μ L and involved mostly men.

In a study by Paul et al. [23] in Nairobi, Kenya, two HIV-

positive patients had clinical signs of the infection and positive blood cultures for *B. melitensis*. One case had acute infection and another had chronic brucellosis. Of the 100 patients referred to the clinic, 65 were HIV positive. All of them had negative blood cultures for *Brucella* and were also examined through ELISA. Eight patients were immunoglobulin (Ig) M and IgG positive for brucellosis. Six patients were positive for IgM, and 21 patients were positive for IgG. However, no relationship was observed between the antibodies and *Brucella* and HIV infection, and the rate of brucellosis infection did not differ in HIV-positive and HIV-negative patients.

Previous studies have shown that *Brucella* is not associated with HIV infection, and immune deficiency does not predispose patients to *Brucella* infection [24].

In conclusion, after observing 157 HIV-positive patients, no cases of brucellosis were reported, and only five (3.2%) patients with low titer and no clinical signs of brucellosis had positive Wright and Coombs Wright test results. Therefore, patients had subclinical forms of brucellosis, and this finding was approximately equal to 3% of the prevalence of brucellosis in Iran [25]. Thus, according to previous studies and the present study, the risk of *Brucella* infection in HIV-positive patients is not higher than healthy that of individuals, even in areas with a high prevalence rate.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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