



Undiagnosed Brucellosis in Psychiatric Patients: A Cross-Sectional Study

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Abstract

Background: Brucellosis, also known as malt fever, poses significant health and economic challenges across various regions worldwide, particularly in Mediterranean and Middle Eastern countries.

Objectives: This study aimed to identify cases of undiagnosed brucellosis among psychiatric patients.

Methods: This descriptive cross-sectional study was conducted at Golestan Hospital in Ahvaz, Khozestan Province, Iran. The study aimed to investigate cases of undiagnosed brucellosis among psychiatric patients during the first 6 months of 2021. The diagnosis of brucellosis relied on standard tests, namely the Wright test, the Coombs-Wright test, and the two-mercaptoethanol test, which are widely recognized as reference techniques. In the endemic region of Iran, a positive titer of at least 1: 80 in the Wright test and titers of at least 1: 40 in the two-mercaptoethanol test are considered diagnostic criteria. The Coombs-Wright test is deemed positive when the titer is 3 dilutions higher than the Wright test titer in symptomatic patients.

Results: A total of 225 patients admitted to psychiatric wards with psychiatric disorders underwent examination for brucellosis. The study revealed an undiagnosed brucellosis prevalence of 7.6% (n = 17). None of these patients had a recent or prior history of brucellosis, nor had they received any treatment for the disease. Among the 17 patients, 3 reported experiencing typical and commonly observed symptoms of brucellosis, such as myalgia and arthralgia, during the clinical interviews. However, the remaining 14 patients did not display any clinical symptoms typically associated with brucellosis, including myalgia, arthralgia, fever, and sweating. Instead, they solely exhibited psychiatric symptoms alongside their condition.

Conclusions: Out of the 225 patients who were diagnosed with psychiatric disorders, 17 individuals were found to have brucellosis. Remarkably, 14 out of these 17 patients did not exhibit typical symptoms associated with brucellosis, but rather only showed psychiatric symptoms as manifestations of the disease.

Keywords: Brucellosis, Psychiatry, Coombs Test, Mercaptoethanol, Fever

1. Background

Brucellosis, commonly known as malt fever, poses significant health and economic challenges in various regions worldwide, particularly in Mediterranean and Middle Eastern countries. According to the World Health Organization, the global annual incidence of new brucellosis cases exceeds 500,000 (1). While developed countries have managed to control brucellosis to a great extent, it continues to be a significant healthcare concern in developing nations (2). *Brucella*, the causative agent of brucellosis, is a small, non-motile, gram-negative coccobacillus that lacks spores and thrives in aerobic conditions (3).

Brucellosis is a bacterial infection that can affect humans and is typically transmitted through the consumption of raw dairy or meat products, as well as through direct contact with infected animals or inhalation of contaminated particles in the air. Individuals working with animals or in related industries, such as veterinarians or slaughterhouse workers, face a higher risk of contracting the disease (4). Iran has experienced endemicity of brucellosis for several years, particularly in the Central Province, where the incidence rate ranges from 98 to 130 cases per 100,000 individuals. The presence of "severe pollution" is a contributing factor within the community (5). According to the Ministry of Health's 2013

statistics, the incidence rate of brucellosis in Kohgilouye and Boyer-Ahmad provinces accounted for 28% of the population, whereas in Fars, Khuzestan, and Bushehr provinces, the rates were 5%, 7%, and 25%, respectively (6).

Brucellosis can manifest in humans in various forms, including acute, sub-acute, chronic, and localized. The incubation period for this disease ranges from 1 to 6 weeks or even several months (1-14 months). Acute brucellosis is characterized by symptoms such as fever, chills, headache, muscle and joint pain, weakness, fatigue, nausea, night sweats, and loss of appetite. It is important to note that brucellosis is a systemic disease known to affect multiple systems in the body, including the digestive, cardiovascular, hematopoietic, skeletal, pulmonary, skin, eye, and nervous systems (7).

Neurological involvement, known as "neurobrucellosis," is observed in less than 5% of individuals affected by brucellosis. Among these cases, meningitis is considered the most common neurological disorder (8). Additionally, neurobrucellosis can manifest in other forms, such as encephalitis, brain abscess, epidural abscess, brain vessel involvement, cerebral nerve paralysis, and brain granuloma. Psychiatric symptoms such as depression, anxiety, excitability, dementia, and euphoria have also been reported in patients with neurobrucellosis (9). Given that psychiatric patients often have compromised immune systems, they may be more susceptible to contracting brucellosis. It is crucial to raise awareness among healthcare professionals, particularly those working in psychiatric settings, about the risk of brucellosis among patients with psychiatric disorders. This awareness can facilitate early diagnosis and treatment, potentially reducing the likelihood of long-term complications and improving patient outcomes. Recognizing the potential presence of undiagnosed brucellosis in psychiatric patients enables healthcare professionals to take necessary measures to prevent disease transmission and ensure appropriate care and treatment (10).

2. Objectives

This study specifically aimed to investigate cases of undiagnosed brucellosis among psychiatric patients.

3. Methods

3.1. Study Design

This cross-sectional descriptive study was conducted in Ahvaz, Khuzestan, Iran, from March to September 2021. The study protocol received approval from the Institutional

Review Board (IRB) of Jandshapur University of Medical Sciences (IR.AJUMS.HGOLESTAN.REC.1399.147). Participants were selected using an available sampling method, which involved recruiting patients referred to the psychiatry department of Golestan Hospital within the age range of 18 to 75 years during the study period. Pregnant women and individuals younger than 18 years or older than 75 years were excluded from the study. The response rate was 100%, with 225 participants completing the study. All psychiatric patients diagnosed with depression, psychosis, bipolar disorder, or any other psychiatric disorder with acute or chronic onset, as determined by the psychiatrist using the SCID-V scale, were included in the group of psychiatric diseases. These patients required hospitalization for disease management based on the psychiatrist's diagnosis.

3.2. Study Procedure

Patients received daily visits from their attending psychiatrists throughout their hospitalization. As part of routine procedures on the first day of admission, blood samples were collected from all patients for initial and basic tests. To minimize the need for additional blood draws, 5 cc clots were obtained from each patient selected for inclusion in the study, specifically for brucellosis diagnostic tests.

All patients received suitable psychiatric treatment and care as determined by the attending psychiatrist. The collected clots for testing purposes were transported to a private laboratory at the researcher's expense, without any additional fees charged to the patients, while ensuring adherence to proper cold chain and handling protocols. The tests conducted for the patients included Wright/2ME/Coombs-Wright, as advised by the infectious disease specialist. Patients who tested positive were treated at no extra cost, following the doctor's recommendations and treatment protocol.

For conducting the Wright test, the patient's blood sample is initially subjected to centrifugation to separate the serum. Next, the obtained serum is mixed with *Brucella* antigen (utilizing antigen kits from the Pasteur Institute of Iran) on a slide. Varying amounts of serum are applied to different areas of the slide, followed by the addition of antigens. After thoroughly mixing the serum and antigen, the test result (presence or absence of agglutination) is determined by observing the slide for agglutination after 1 minute.

In the case of a positive result in the Wright test, a titration test, also known as a tube test, is employed to determine the antibody titer. In this test, serum dilutions of 1: 20, 1: 40, 1: 80, 1: 160, and so on (with doubling dilutions based on the level of positivity) are prepared in tubes using normal saline. Following

this, specific antigens are added to all the tubes and incubated for 24 hours at a temperature of 37°C. After the 24-hour incubation period, the tubes are examined for the presence of agglutination. The highest dilution showing agglutination corresponds to the patient's antibody titer. In Iran, a titer of 1: 80 or higher indicates a positive result.

Following the completion of the Wright test, each positive sample underwent the 2ME test to determine the antibody class. In this test, the disulfide bonds within the IgM structure are disrupted using a substance called 2-mercaptoethanol (2ME), effectively eliminating all existing IgMs within the patient's serum. Subsequently, the test continued using the serum devoid of IgM, employing the tube agglutination method with multiple dilutions. Finally, 2ME-specific antigen was added to all tubes. Following a 24-hour incubation period at 37°C, the highest dilution showing agglutination was recorded as the 2ME titer.

The Coombs-Wright test method was employed to detect the presence of blocking antibodies, which are known to increase during the chronic phase of brucellosis. These particular antibodies are characterized by their inability to cause agglutination upon reacting with *Brucella* antigen, hence being referred to as incomplete antibodies. After performing the Wright test, samples that did not exhibit agglutination were further examined to identify the presence of blocking antibodies. The Coombs-Wright test, utilizing kits from the Pasteur Institute of Iran, was conducted for this purpose. These kits contain antibodies that specifically bind to the tails of antibodies (while the heads of the antibodies are attached to the antigen). By doing so, adjacent antibodies attached to the antigen are connected, leading to agglutination through these antibodies.

The Wright/2ME/Coombs test was conducted based on the recommendation of an infectious disease specialist. No charges were incurred by the insurance or the patients for the required tests. Patients who tested positive received treatment in accordance with the doctor's advice and treatment protocol without any additional expenses.

3.3. Statistical Analysis

The statistical analysis was performed using SPSS version 26. Statistical significance was assessed by setting the alpha level below 5 percent. An independent t-test was utilized to compare the ages of the infected and non-infected patient groups. To explore the association between Brucellosis status and categorical variables such as sex, marital status, employment status, and type of psychiatric disorder, the chi-square test (or Fisher's exact test, if required) was employed.

4. Results

In this study, a total of 225 patients were included for evaluation. Among the studied population, 60% were male, while 40% were female. Regarding marital status, 66.2% of patients were single, and 32% were married. Regarding employment status, 41.8% of patients were unemployed, 36.9% were housewives, and 17.3% held jobs in the market sector, such as shopkeepers (Table 1).

In this study, a total of 225 patients with psychiatric disorders, who were hospitalized in psychiatric wards, were examined to investigate the association between brucellosis and psychiatric diseases. None of these patients had a recent or previous history of brucellosis, nor had they received any treatment for the disease. All 225 patients underwent brucellosis diagnostic tests, out of which 208 patients tested negative, while 17 patients were diagnosed with brucellosis based on laboratory findings. During clinical interviews, 3 out of these 17 patients exhibited typical and common symptoms of brucellosis, including myalgia and arthralgia. On the other hand, the remaining 14 patients did not report any common clinical symptoms of brucellosis, such as myalgia, arthralgia, fever, or sweating. Instead, they solely presented psychiatric symptoms as accompanying manifestations.

Therefore, while acknowledging the limitations of this study due to the absence of a control group, it is important to note that the presence of brucellosis with psychiatric symptoms in 14 patients highlights the need for further investigation into this relationship through future studies incorporating a control group.

The prevalence of undiagnosed brucellosis was 7.6%.

The findings indicate no statistically significant relationship between the type of psychiatric disorder and *Brucella* infection, as shown in Table 2 ($P = 0.490$). Furthermore, among the patients with *Brucella* infection, 76.5% reported consuming non-pasteurized dairy products, while 23.5% did not consume such products. Similarly, among the *Brucella*-negative patients, 78.8% consumed non-pasteurized dairy products, while 21.2% did not. However, there was no statistically significant relationship between the consumption of non-pasteurized dairy products and brucellosis ($P = 0.760$).

Marital status ($P = 0.821$), place of residence ($P = 0.593$), and gender ($P = 0.141$) were not found to have a significant relationship with brucellosis. However, a significant relationship was observed between patients' employment status and brucellosis ($P = 0.041$). Among the non-infected individuals, 38.5% were unemployed, whereas 82.4% of those with brucellosis were unemployed.

Table 1. Demographics of Patients

Variables	No. (%)
Gender	
Male	135 (60)
Female	90 (40)
Marital status	
Single	149 (66.2)
Married	72 (32)
Widow	4 (1.8)
Job	
Unemployed	94 (41.8)
Hospital	3 (1.3)
Livestock	2 (0.9)
Market	39 (17.3)
Official	1 (0.4)
Structural	3 (1.3)
Housewife	83 (36.9)
Place of living	
Urban	156 (69.3)
Rural	61 (27.1)
Prison	8 (3.6)
Types of psychiatric disorders	
Schizophrenia	97 (43.1)
Bipolar disease	92 (40.9)
Major depression disease	36 (16)
Consumption of non-pasteurized dairy products	
Positive	177 (78.7)
Negative	48 (21.3)
Wright agglutination test	
Negative	219 (97.3)
1/40	3 (1.3)
1/80	3 (1.3)
2 ME	
Negative	225 (100)
Coombs wright	
Negative	190 (84.4)
1/20	1 (0.4)
1/40	19 (8.2)
1/60	1 (0.4)
1/80	14 (6.2)
Brucella	
Negative	208 (92.4)
Positive	17 (7.6)

5. Discussion

Brucellosis, also known as malt fever, is a highly contagious disease that affects both humans and animals. The primary modes of transmission to humans include consuming unpasteurized milk, raw or undercooked meat, and close contact with the body secretions of infected animals. It is widely acknowledged that chronic brucellosis can manifest as a neuropsychiatric disorder, a concept emphasized by Spink (1963) in Cecil and Loeb's Medical Reference (11).

In this study, the prevalence of brucellosis among patients was found to be 7.6%. Notably, all patients with a positive Wright titer exhibited clinical symptoms. Neurobrucellosis can manifest at any stage of the disease and present with diverse manifestations, such as encephalitis, meningoencephalitis, subarachnoid hemorrhage, and psychiatric symptoms (12, 13). Previous studies have also reported on the association between mental disorders and brucellosis (14, 15).

Our findings revealed no significant differences in sociodemographic characteristics among undiagnosed brucellosis patients. Gender, previous history of any type of brucellosis, and place of residence did not show a significant relationship with brucellosis. However, a study conducted by Aloufi et al. (16) reported a higher infection rate in men, particularly in the age group of 15 to 45 years. Additionally, the study found a higher infection rate in endemic (rural) areas compared to other areas. These findings are contradictory to the results of our study. One possible explanation for this disparity could be attributed to 2 methodological factors in the previous study. Firstly, they examined a larger population sample size of 19,130 individuals, whereas our study had a smaller sample size. Secondly, the duration of their study spanned over 8 years, from 2004 to 2012, whereas our study was conducted within a limited timeframe of 6 months. It is worth noting that a study conducted in Africa (17) reported a brucellosis prevalence rate of 7.8% over a 6-month period (March to August 2013). However, it is important to highlight that their study focused specifically on the population at the slaughterhouse, which may have contributed to the differences observed. Hence, it can be concluded that the prevalence rates of brucellosis appear to be influenced by the characteristics of the study population. Similar to our findings, the study conducted by Hashtarkhani et al. (18) also reported that 85% of patients resided in rural areas, while 15% lived in urban areas. The prevalence rate was found to be 43.1% in women and 56.9% in men, aligning with our results. Although men had a slightly higher prevalence rate, it was not significantly associated with infection. Our study did not

Table 2. Association Between *Brucella* and Disease Characteristics

Characteristics	<i>Brucella</i>		P-Value
	Positive (N = 17), No. (%)	Negative (N = 208), No. (%)	
Type of psychiatric disorder			0.490
Schizophrenia	8 (3.6)	89 (39.6)	
Bipolar disease	8 (3.6)	84 (37.3)	
Major depression disease	1 (2.8)	35 (15.6)	
Consumption of non-pasteurized dairy products			0.760
Positive	13 (5.8)	164 (72.9)	
Negative	4 (1.8)	44 (19.6)	
Marital status			0.821
Single	11 (4.9)	138 (61.3)	
Married	6 (2.7)	66 (29.3)	
Widow	0 (0)	4 (1.8)	
Residence place			0.593
Urban	10 (4.4)	146 (64.9)	
Rural	6 (2.7)	55 (24.4)	
Prison	1 (0.4)	7 (3.1)	
Sex			0.141
Male	13 (5.8)	122 (54.2)	
Female	4 (1.8)	86 (38.2)	

find a significant relationship between the consumption of non-pasteurized dairy products, such as milk, yogurt, and cheese, and brucellosis. In a study carried out in Iran in 2008 (19), significant risk factors for brucellosis infection were identified as having another brucellosis case in the household (odds ratio 7.55) and consuming unpasteurized dairy products (odds ratio 3.7). Cattle rearing and the practice of cattle vaccination were identified as significant risk factors. Our study results indicated that although more than two-thirds of brucellosis patients reported consuming unpasteurized dairy products, no significant association was observed between the consumption of such products and brucellosis. This finding aligns with a similar study conducted in Iran. In the study by Eren et al. (20), it was concluded that there is no significant correlation between the consumption of unpasteurized milk and the incidence of brucellosis, regardless of the presence of neurological symptoms. This finding further supports the results of our study.

Based on a review report (21), the majority of brucellosis cases were attributed to traditional risk factors such as travel or the consumption of unpasteurized dairy products in endemic countries. Additionally, cases related to the importation of food products or

infected animals have also been documented. While the prevalence of melitensis is generally lower in developed countries, certain populations within these countries, such as Hispanic patients in the United States and Turkish immigrants in Germany, may still exhibit a higher incidence. Imported brucellosis, transmitted by immigrants, presents with diverse manifestations, both typical and atypical, which can result in misdiagnoses and delays in diagnosis.

In our study, a significant relationship was observed between individuals' job types and brucellosis, with a higher prevalence among unemployed individuals. Therefore, occupation appears to be a significant factor associated with brucellosis. However, it is important to note that our study focused specifically on patients seeking psychiatric care who may have different employment patterns due to the social consequences of the disease. These patients often experience underemployment or stay at home as a result. It is worth mentioning that this dynamic may differ in a typical population setting. A study conducted in Turkey (22) identified working in private veterinary clinics, male gender, the number of animal deliveries performed, and injuries during *Brucella* vaccine administration as risk factors for occupational

brucellosis. Consequently, brucellosis has been proposed as an occupational disease.

5.1. Limitations and Suggestions

The current study had certain limitations that should be acknowledged. Firstly, the study was conducted exclusively at Golestan Hospital in Ahvaz, which limits the generalizability of the findings to a broader population. Additionally, this study was conducted as a single-center study, potentially introducing biases associated with a specific hospital setting. Secondly, the investigation period for this study was limited to 6 months, and it is advisable for future studies to consider a longer duration for more comprehensive results. Thirdly, the sample size of the study was moderate, and future studies with larger sample sizes should be conducted to enhance statistical power and strengthen the conclusions.

5.2. Conclusions

No significant associations were found between brucellosis and gender, age, place of residence, or consumption of non-pasteurized dairy products. However, a notable correlation was observed between individuals' employment status and brucellosis, with a higher prevalence among the unemployed population. Furthermore, no significant relationship was identified between brucellosis and psychiatric disorders. It is worth noting that among the psychiatric patients included in the study, 14 individuals exhibited atypical symptoms suggestive of undiagnosed brucellosis.

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Footnotes

Authors' Contribution: Study concept and design: S. M., H. R., S. S., M. C., F. T. Acquisition of data: F. T. Analysis and interpretation of data: S. M., H. R., S. S., M. C., F. T. Drafting of the manuscript: S. M., H. R., S. S., M. C., F. T. Critical revision of the manuscript for important intellectual content: S. M., H. R., S. S., M. C., F. T. Statistical analysis: S. M., H. R., S. S., M. C., F. T. Study supervision: S. M.

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Data Reproducibility: The dataset is available for scientists and researchers in the medical field upon reasonable email requests to the corresponding author.

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