

Psychiatric Effects of Brucellosis: A Little-Known Aspect of an Ancient Disease

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Abstract

Brucellosis is a zoonotic disease that can lead to a variety of clinical manifestations. This disease, which is endemic in Mediterranean countries including Turkey, is of interest to many specialties due to its multisystem involvement. In this article, we aimed to investigate the lesser-known aspects of brucellosis by examining the psychiatric symptoms associated with this old and persistent disease, to review the published literature on a global level, and to reveal the contribution from our country. Beyond the physical burden of brucellosis, it is crucial to recognize and address the psychiatric effects that this disease can have on individuals. By raising awareness about the psychiatric aspects of brucellosis, healthcare providers can implement comprehensive care strategies that encompass both physical and mental health support. Integrating psychiatric assessment, counseling and appropriate pharmacological interventions is essential to reduce the negative psychiatric impact of brucellosis and promote holistic recovery. Once understood primarily as a physical disorder, the potential impact of brucellosis on mental health is now recognized. The psychiatric effects of brucellosis can range from mood disorders and cognitive impairment to psychotic symptoms and sleep disturbances. Understanding the mechanisms and risk factors underlying these psychiatric symptoms is vital for developing effective interventions and providing holistic care. By shedding light on this often-overlooked aspect of brucellosis, medical professionals can improve patient outcomes and enhance the quality of life of those affected by this infectious disease.

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1. Introduction

Brucellosis is a zoonotic infectious disease caused by the bacteria of the *Brucella* genus. This genus is Gram-negative, facultative intracellular bacteria (Zheng et al.,2018; Arslan et al.,2023; Hayoun et al.,2023).

Remitting fever, undulant fever, Mediterranean fever, Maltese fever, Gibraltar fever, Crimean fever, goat fever, and Bang disease are just a few of its other names (Hayoun et al.,2023). Brucellosis is still endemic in most of the world, but after extensive and expensive control programs, it has been virtually eliminated from livestock in much of Northern Europe, Australia, the United States, and Canada. All of the major agricultural animal species are vulnerable, and the presence of wildlife reservoirs in some areas makes complete control difficult (Thorne et al.,1978). According to the World Health Organization (WHO), brucellosis is a serious illness that affects people all over the world, but it is particularly prevalent in the Mediterranean region of Europe, North and East Africa, the Middle East, South, and Central Asia, and Central and South America (Corbel, 2006). Brucellosis is prevalent in Turkey, making it one of the countries where the disease is endemic (Güven et al.,2013). According to the WHO, there are around 500,000 brucellosis new cases annually worldwide and 10,000–20,000 cases per year in Europe (World Health Organization,2014). Therefore, the disease is primarily either occupational, being associated with farmers, veterinarians, abattoir workers, and laboratory personnel, or is associated with travelers returning from endemic areas in more developed parts of the world where stricter food hygiene measures may be practiced (Young, 2010; Gul&Erdem,2015). Brucellosis primarily affects livestock, such as cattle, goats, and sheep, but can be transmitted to humans through direct contact with infected animals, consumption of contaminated dairy products, or inhalation of airborne particles. Once inside the body, the bacteria primarily target the reproductive organs, causing symptoms such as fever, fatigue, joint pain, and muscle aches (Zheng et al.,2018; Hayoun et al.,2023). However, recent research has shed light on the psychiatric effects toll brucellosis can take on infected individuals (Eren et al.,2006; Gulet al.,2009; de Figueiredo et al.,2015).

Due to *Brucella*'s ability to adapt to intracellular conditions and outwit the host's natural immune defenses, they are facultative intracellular parasites that can survive inside host cells after phagocytosis. This chronic infection is a result of this ability (Shehata et al.,2010). Brucellosis can last for several days or even years, but because it is frequently misdiagnosed, it can result in ineffective treatment and a protracted illness (Zheng et al.,2018).

In previously healthy patients, brucellosis is typically not fatal, but if untreated, it can result in a chronic infection with incapacitating recurrent clinical episodes (Young, 2010; Gul&Erdem,2015). Five of the 10 species that make up the genus *Brucella* have been found to be pathogenic in humans (Bouferraa et al.,2021). *Brucella abortus*, *Brucella melitensis*, *Brucella suis*, and *Brucella canis* infections frequently lead to human cases of brucellosis (Young, 2010; Gul&Erdem,2015).

The diagnosis of brucellosis relied on the presence of consistent clinical findings and either a serum agglutinin titer of $\geq 1:160$ in serum tube agglutination (STA) or a positive blood culture (Gul&Erdem,2015).

A wide variety of clinical manifestations may occur as a result of the multisystemic disease brucellosis (Arslan et al.,2023). The most common signs of human infections include fever, malaise, sweats, and lymphadenopathy. However, they can also cause serious complications like endocarditis, meningoencephalitis, arthritis, spondylitis, orchitis, and psychological distress (Young, 2010; Gul&Erdem,2015). While the physical symptoms of brucellosis are well-documented (Zheng et al.,2018; Hayoun et al.,2023), its psychiatric effects often remain overlooked and understudied. However, in recent years, medical experts have begun to recognize that this bacterial infection can also exert significant effects on mental health. The psychiatric implications of brucellosis have become an emerging area of research, shedding light on the hidden impact this disease can have on individuals' psychological well-being (Eren et al.,2006; Gulet al.,2009; de Figueiredo et al.,2015). This article delves into the psychiatric effects of brucellosis, exploring the potential mechanisms, risk factors, and implications for both patients and healthcare professionals.

1.1. Understanding Neurobrucellosis

Neurobrucellosis represents a significant complication that can arise from systemic brucellosis infection (McLean et al.,1992). It was reported that, Florence Nightingale's chronic and severe headaches might have been attributed to a historically significant disease, possibly brucellosis (Young,1995).

The central nervous system may be affected by *Brucella spp.* either directly through invasion of neural tissue or indirectly through endotoxins or immune-inflammatory responses triggered by the bacteria's presence in the body (Bouferraa et al.,2021). Soares et al reported that the incidence of neurobrucellosis is about 4%, and it is virtually always diverse (Soares et al.,2023). In the literature, the occurrence of neuro brucellosis has been

reported with a wide range, varying from 0.5% to 25% (Shakir et al.,1987; Lubani et al.,1989).

An increased risk of nervous system involvement in brucellosis exists in older patients (Bouferraa et al.,2021).

In the majority of cases, the diagnosis of neurobrucellosis is typically established between 2 to 12 months after the initial onset of symptoms (Sanchez-Sousa et al., 1990; Akdeniz et al.,1998). Since it lacks normal clinical signs, other infections frequently mistakenly diagnose it (Soares et al.,2023). The patients may also experience general nonspecific neurological and psychiatric symptoms (Bouferraa et al.,2021).

Meningitis, meningoencephalitis, encephalitis, cranial neuropathies, intracranial hypertension, sinus thrombosis, hemorrhages' radiculitis, peripheral neuropathy, myelitis, and psychiatric symptoms are all included in the neuro brucellosis presentation (Soares et al.,2023).

The diagnosis ought to be made on the basis of neuro brucellosis-specific symptoms and indications that cannot be explained by another neurological condition (Soares et al.,2023). But, the diagnostic criteria for neurobrucellosis pose challenges in the literature. Some authors argue that the diagnosis should rely on clinical neurological symptoms, while others suggest that microbiological and/or biochemical evidence from cerebrospinal fluid should be the basis for diagnosis (Sanchez-Sousa et al., 1990; Bodur et al.,2003; Eren et al.,2006; Yetkin et al.,2006; Karsen et al.,2007).

There are four diagnostic criteria for the diagnosis of neurobrucellosis, which include signs and symptoms suggestive of neurobrucellosis, a positive finding of *Brucella spp.* in the cerebrospinal fluid (CSF), and/or a positive titer of antibodies targeting *Brucella* in the CSF, lymphocytosis with high protein levels and low glucose levels in CSF, and imaging findings (either cranial magnetic resonance imaging or computed tomography) peculiar to neurobrucellosis (Bouferraa et al.,2021).

According to a study from Turkey, agitation (25%), abnormal behavioral patterns (25%), muscle weakness (23%), disorientation (21%), and neck rigidity (17%) were the most prevalent neurological findings, among 128 laboratory-confirmed brucellosis cases who had neurological symptoms, and 48 (37.5%) had neurobrucellosis diagnosis (Guyen et al.,2013).

1.2. Physical Symptoms vs. Psychiatric Manifestations

While brucellosis is commonly known for its physical symptoms, such as fever, sweating, fatigue, and joint pain (Hayoun et al.,2023), there is an

emerging body of evidence suggesting that the disease can also impact the central nervous system and mental health (Eren et al.,2006; Gulet al.,2009; de Figueiredo et al.,2015). Psychiatric symptoms associated with brucellosis may vary widely, and the severity and presentation can depend on factors like the strain of *Brucella*, individual susceptibility, and the stage of infection (Bourne et al.,1964; McDevitt,1973; Eren et al.,2006; Gulet al.,2009; de Figueiredo et al.,2015;Esmael et al.,2021).

According to a study, 2 out of 500 nonpsychiatric patients and 3 out of 500 newly diagnosed psychiatric patients with no suspicious brucellosis findings had positive serologic tests. Even though this complication is uncommon, the higher community prevalence of brucellosis leads to the consideration of brucellosis as a significant option in the differential diagnosis of psychiatric symptoms. This study emphasizes that brucellosis should be considered in the differential diagnosis for any psychiatric patient who exhibits psychiatric symptoms, particularly in endemic brucellosis areas (Shoaei&Bidi,2012). According to a study conducted on 400 brucellosis patients in Kuwait, 6% of those individuals experienced psychiatric complications, primarily depression and anxiety during the chronic stage of the illness. According to one study, patients with emotional disorders who did not have acute or chronic brucellosis were found to have *Brucella* deoxyribonucleic acid (DNA) in their blood. Out of 20 patients with emotional disorders, 3 (15%) had *Brucella* DNA found; however, all the controls tested negative (Kechagia et al.,2011).

According to the study conducted by Zou et al, it was observed that the patient's emotional changes, including mood disorder, feelings of sadness, and loss of interest, exhibited slight improvement after undergoing anti-depression therapy. However, these emotional changes were further alleviated through antibiotic therapy. Based on the patient's epidemiological history and the psychiatric manifestations observed after intermittent fever, it was hypothesized that the patient's depression could be attributed to brucellosis. Despite negative cranial magnetic resonance imaging scans and absence of neurological signs, the connection between brucellosis and the psychiatric symptoms was considered (Zhou et al.,2023).

In Eren et al's study (Eren et al.,2006), a total of 34 cases of neurobrucellosis and 30 patients with brucellosis but without neurological involvement were examined. Two psychiatrists conducted interviews with the patients and administered the Hamilton Depression Rating Scale (HDRS) and Mini-Mental State Examination (MMSE) tests. Among the neurobrucellosis cases, the mean MMSE score before antibiotic therapy was 21.6. One week

after therapy, it increased to 22.7, and after two weeks of therapy, it further improved to 24.3 ($p=0.024$ and $p<0.001$, respectively). The mean HDRS score at the time of admission before therapy was 9.9, which decreased to 7.8 after one week of therapy, and reached 5 after two weeks of therapy ($p=0.014$ and $p<0.001$, respectively). The study reported that cognitive and emotional disturbances in neurobrucellosis patients were assessed using the MMSE and HDRS tests. These disturbances showed improvement with antibiotic therapy alone, without the need for additional antidepressant or antipsychotic therapy (Eren et al.,2006).

1.3. The mechanisms underlying the neuropsychological manifestations of brucellosis

Increasing levels of cytokines and microbial-derived antigens in the blood may change the body's neuro-immune balance and, consequently, the behavior, even though the mechanisms underlying the neuropsychological manifestations of brucellosis are unclear (Dantzer,2009; Miller et al.,2013; Pavlov&Tracey,2017; Salvador et al.,2021).

However, the observation that functional sequela occurs in patients with chronic brucellosis supports the possibility that this is the case (Shehata et al.,2010).

The majority of patients advance to a chronic stage of the disease where neuropsychiatric symptoms worsen. It is still unknown what biological mechanisms underlie the development of these symptoms. Localized inflammation brought on by *Brucella* may cause neurochemical changes and, as a result, unrestrained neuropsychiatric disorders. According to the findings of an experimental mouse study, motor impairments, muscular weakness, and decreased motivation in *Brucella* -infected mice were correlated with neurochemical and peripheral immunological disturbances and tended to diminish after 21 days of infection. The current data in this report supported the hypothesis that mood disorders in infected mice may result from disturbed peripheral inflammation and associated neurochemical disruption (Maldonado-García et al.,2021).

1.4. Psychiatric Effects of Brucellosis

1.4.1. Depression and Anxiety

Depression and cognitive impairment are commonly observed symptoms in cases of brucellosis. However, depression stands out as the most prevalent psychiatric disorder and often appears to be disproportionate to the severity

of other symptoms experienced (Shakir et al.,1987; McLean et al.,1992; Akdeniz et al.,1998; Bodur et al.,2003; Young,2010; Shoaci&Bidi,2012; Elzein et al.,2018; Zhou et al.,2023). Brucellosis can significantly impact an individual's mental health. Studies have shown that the chronic nature of the infection, coupled with the prolonged physical symptoms, can lead to the development of depressive symptoms. Feelings of sadness, hopelessness, and anhedonia (inability to experience pleasure) may be present. Additionally, anxiety disorders, such as generalized anxiety disorder and panic disorder, can emerge due to the uncertain and protracted nature of the illness (Bourne et al.,1964; McDevitt,1973; Esmael et al.,2021).

In one study, 50 healthy matched controls and 27 brucellosis patients were compared. 14 (51.9%) of the patients with brucellosis had overt or apparent neurological manifestations, while the remaining 13 (48.2%) did not appear to have any neuropsychiatric involvement. A total of 7 patients (29.2%) had depression (Shehata, et al.,2010).

In a different study, two psychiatrists conducted interviews with the neurobrucellosis patients and administered the MMSE and HDRS tests (Hamilton Depression Rating Scale). There was no antidepressant or antipsychotic therapy used to treat the documented cognitive and emotional disturbances that were improved by antibiotic therapy (Eren et al.,2006).

According to a recent study, patients diagnosed with neurobrucellosis exhibited elevated levels of psychiatric symptoms, including behavioral changes, anxiety, and depression ($p < 0.001$, $p < 0.001$, and $p: 0.01$, respectively), and considerably poorer cognition than non-neurobrucellosis patients (Esmael et al.,2021).

1.4.2. Cognitive Impairment

Brucellosis has been associated with cognitive impairment, including difficulties with concentration, memory loss, and decreased processing speed. These cognitive deficits can impact daily functioning, work performance, and overall quality of life. The precise mechanisms behind these effects are not fully understood but may be related to the inflammatory response and neurotoxicity caused by the bacteria (Shehata, et al.,2010; Liapina, et al.,2010; Smagina&Shul'diakov,2011).

In a recent study, indices of the quality of life and psycho-functional status parameters of patients with chronic active brucellosis have been identified, and for a group of 40 patients, the therapeutic effectiveness of the immunomodulator cycloferon in the complex treatment of the disease was evaluated. Twenty of the individuals received cycloferon, whereas the other

twenty patients in the control group solely received conventional treatment. It is known that the dimensions of one's quality of life significantly decline when one has chronic active brucellosis. In comparison to results obtained with conventional therapeutic techniques, the administration of cycloferon against the backdrop of a base therapy improves the quality of life and psychoemotional status markers (Smagina&Shul'diakov,2011).

Another study looked at the therapeutic potential of cyclopheron via chronic brucellosis patients as an example. Improvements in quality of life, a decrease in the frequency of exacerbations of the infectious process, and the emergence of concurrent diseases are all positive clinical dynamics during combination therapy with cyclopheron. It has been established that these effects result from cyclopheron's immunomodulating activity and its suppression of lipid peroxidation. Additionally, the medication boosts antioxidant activity while lowering pro-inflammatory (and, to a lesser extent, anti-inflammatory) cytokine levels (Liapina, et al.,2010).

A controlled clinical trial examined the clinical and pathogenetic efficacy of cytoflavin as a component of the combined therapy for chronic brucellosis in 50 patients, who also confirmed the drug's positive impact on quality of life. Based on this study's findings, cytoflavin serves by lessening the severity of endogenous intoxication and systemic inflammation (Shul'diakov et al.,2011).

1.4.3. Sleep Disturbances

Brucellosis can disrupt normal sleep patterns, leading to insomnia or excessive daytime sleepiness. The physical discomfort, pain, and anxiety associated with the infection can interfere with sleep initiation and maintenance. Sleep disturbances, in turn, exacerbate psychiatric symptoms and contribute to an overall decline in mental well-being (Malik et al.,2018; Mansurova&Nazarov,2021; Alimovna,2023). In a study of 70 brucellosis patients, insomnia was found in 12.9% of patients (Malik et al.,2018). Laziness, distractibility, sudden, uncontrollable urges to sleep, and a reversal of the typical sleep-wake cycle are all signs of sleep disturbances. Without treatment, the disease advances to a terminal stage characterized by seizures, extreme somnolence, double stim, cerebral edema, coma, systemic organ failure, and death (Duggan&Hutchington,1966).

1.4.4. Psychosis

Brucellosis can occasionally develop neuro brucellosis, which affects both the central and peripheral nervous systems and can have serious clinical

effects (Eren et al.,2006; Ates et al.,2008; Ghaffarinejad et al.,2008; Shehata et al.,2010).

Although psychiatric findings are uncommon in brucellosis, endemic countries' higher brucellosis prevalence leads to the consideration of brucellosis as a significant alternative in the differential diagnosis of psychiatric symptoms. It is uncommon for neurobrucellosis to present with psychosis. Only a few prior reports of brucellar psychosis were available in the current literature (Ates et al.,2008; Ghaffarinejad et al.,2008).

1.4.5. Post-Traumatic Stress Disorder (PTSD)

Although chronic post-traumatic stress disorders are numerous and diverse, post-traumatic stress disorder (PTSD) continues to be the most well-known. Posttraumatic depression and bereavement can lead to a heightened risk of suicidal crises and self-harming behaviors. When experiencing post-traumatic anxiety disorders, which may include conditions like agoraphobia, specific phobia, obsessive-compulsive disorder, separation anxiety, or social phobia, individuals often exhibit symptoms of re-experiencing, heightened arousal with increased anxious reactivity, and resort to avoidance strategies that intensify anticipatory anxiety. It is not uncommon for post-traumatic symptoms to co-occur with chronic psychotic manifestations, resulting in a clinical picture that is frequently severe. These may include conditions such as post-traumatic schizophrenia, post-traumatic depression with mood-congruent psychotic features, non-schizophrenic post-traumatic psychotic disorder, and bipolar reaction to trauma. Furthermore, if an injury occurs simultaneously with traumatic exposure, the likelihood of later developing post-traumatic stress disorder is heightened (Nohales&Prieto,2018). This, in turn, affects how the body is perceived to be feeling (development of somatoform and psychosomatic disorders, co-morbidity with post-concussion syndrome). Trauma can cause a person's biography to fall apart, as well as their internal physiological processes and social interactions (impacts of instinctive behaviors, personality changes, and adjustment issues on work and personal life) (Auxéméry,2018; Nohales&Prieto,2018).

Recent research indicates that beyond the conventional psychological and behavioral indicators, PTSD diagnosis now takes into account the connection between this condition and changes in immune and inflammatory responses. Studies in epidemiology have revealed a notable correlation between PTSD and heightened prevalence of physical comorbidities related to immune dysregulation, including metabolic syndrome, atherosclerotic cardiovascular disease, and autoimmune disorders (Hori&Kim,2019).

Brucellosis can be a traumatic experience for some individuals, particularly in cases of severe complications or prolonged treatment. In severe cases, brucellosis can lead to the development of PTSD. Individuals who have experienced a prolonged illness, endured invasive medical procedures, or faced significant physical and emotional challenges associated with the infection may be at higher risk. Symptoms of PTSD may include intrusive thoughts, flashbacks, hypervigilance, and avoidance behaviors (Eren et al.,2006, Shehata et al.,2010; Esmael et al.,2021).

1.4.6. Social Isolation and Stigma

The chronic nature of brucellosis and the associated physical and psychiatric symptoms can lead to social isolation. Individuals infected with brucellosis may face stigma and discrimination due to misunderstandings about the disease's transmission or fear of contagion. This social isolation and stigma can further contribute to the development or exacerbation of psychiatric symptoms (Eren et al.,2006,Shehata et al.,2010;Esmael et al.,2021).

2. Conclusion

Brucellosis, a disease primarily known for its physical symptoms, can also have profound psychiatric effects on affected individuals. Depression, anxiety, cognitive impairments, and PTSD can significantly impact the mental health and well-being of those diagnosed with brucellosis. Recognizing and addressing these psychiatric manifestations is vital to ensure comprehensive care for patients and improve their quality of life. Given the potential psychiatric impact of brucellosis, it is crucial to incorporate mental health assessments into the clinical management of affected individuals. A multidisciplinary approach involving psychiatrists, infectious disease specialists, and primary care physicians is necessary to ensure comprehensive care for patients with brucellosis. Early recognition and treatment of psychiatric symptoms can significantly improve the patient's overall well-being and enhance their ability to cope with the challenges associated with the disease. Future research and collaborative efforts are necessary to enhance our understanding of the psychiatric aspects of brucellosis and develop effective interventions to mitigate its impact on mental health. Furthermore, there is a need for further research to elucidate the underlying mechanisms of the psychiatric effects of brucellosis. Longitudinal studies are warranted to investigate the long-term psychiatric outcomes and the risk factors associated with the development of these symptoms. Additionally, developing targeted interventions, such as psychoeducation, cognitive-behavioral therapy, and psychopharmacological approaches, may help alleviate psychiatric symptoms and enhance the recovery process.

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