

Neurobrucellosis in the West of Iran: A Case Report with Diagnostic Challenges

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Abstract

Brucellosis is a multisystem infection that can involve any organ, including both central and peripheral nervous systems. Neurobrucellosis (NB) is a rare and often misdiagnosed complication of brucellosis, with various and unexplained neurological symptoms. This study reports a challenging case of NB in a 69-year-old man from western Iran. The patient presented with a one-week history of weakness, malaise, lethargy, loss of consciousness, and generalized musculoskeletal pain, followed by two months of cognitive problems, memory disorders, and delusions. Initial workup with cerebrospinal fluid analysis, blood cultures, and serological tests for brucellosis were inconclusive. Neuroimaging revealed hydrocephalus, meningitis, and multiple ischemic lesions. Initial treatment with broad-spectrum antibiotics and antituberculosis medications, for suspected meningitis or tuberculosis, had limited effects. On the 15th day of hospitalization, a serological panel confirmed brucellosis infection by Wright, Coombs-Wright, and 2ME antibody titers, ELISA, and standard agglutination test. Polymerase chain reaction (PCR) further confirmed the final diagnosis with *B. melitensis* detection. Given the diagnosis of NB, a combination therapy with cotrimoxazole, gentamicin, rifampin, and doxycycline was initiated and continued for two weeks. The patient's clinical condition improved significantly, and he was discharged with specific medication and follow-up instructions. After seven months, he achieved complete recovery, with negative serological and PCR tests. This case highlights the diagnostic challenges of NB, particularly in older patients with atypical presentations. A high index of suspicion, especially in endemic areas including western Iran, is crucial for timely diagnosis and initiation of appropriate antibiotic therapy, leading to favorable outcomes.

Keywords: Neurobrucellosis; Zoonotic disease; *Brucella*; Western Iran.

Introduction

Brucellosis is one of the most common zoonotic diseases, widespread among humans and animals. Recently, the incidence rate of brucellosis in Iran has increased.^{1,2} Kurdistan, a province in western Iran, reports a high incidence of brucellosis annually. Between 1999 and 2008, over 10 000 cases of brucellosis being reported in this region.³

Clinically, brucellosis infections can be acute, sub-acute, or chronic, affecting multiple organs.^{4,5} The gastrointestinal, genitourinary, and cardiovascular systems are commonly involved.² Typical clinical manifestations include fever, sweating, body pain, splenomegaly, hepatomegaly, and other systemic symptoms.⁴ However, neurobrucellosis (NB)—which involves both the central and peripheral nervous systems—occurring in 3% to 10% of cases.^{3,4,6,7} Although various signs have been reported, meningitis, encephalitis, and meningoencephalitis are the most common.^{3,6} Given that NB can be insidious and present atypically, diagnosis is often delayed. Furthermore, the chronic progression of neurological complications can lead to NB being misdiagnosed as other diseases, such as tuberculosis. NB is typically diagnosed two to 12 months after symptom onset.⁸

In this report, we present a case of NB referred to our hospital with unexplained neurological symptoms. The case emphasizes the importance of considering NB in patients with unexplained neurological manifestations.

Case Report

A 69-year-old man from Kurdistan province, western Iran, weighing 71 kg, presented with a one-week history of malaise, weakness, lethargy, loss of consciousness, and generalized musculoskeletal pain, which intensified over the past two days. He was admitted to the Tawheed Medical, Educational and Therapeutic center on 20 July 2022. He also reported mild cognitive problems, memory disorders, and delusions over the previous two months, accompanied by malaise and imbalance. The patient's medical history was unremarkable, with no history of alcohol or drug use. He was married and had no family history of significant medical conditions. He had normocytic normochromic anemia and a history of lumbar disc surgery. His vital signs at admission were within normal limits: respiratory rate (RR) = 20 breaths per minute, pulse rate (PR) = 72 beats per minute, temperature (T) = 36.6°C, and blood pressure (BP) = 135/89 mmHg. Blood oxygen saturation (SpO₂) remained stable between 94% and 96% throughout his hospitalization. Ejection fraction (EF) was 50%, and an electrocardiogram (ECG) showed no abnormalities.

After seven days of hospitalization, the patient developed a headache and muscle pain. During this time, diagnostic procedures and supportive and sedating treatments were administered. Laboratory tests revealed pleocytosis in the cerebrospinal fluid (CSF) sample, with lymphocytes accounting for 91% of the leukocytes. The CSF protein concentration was elevated at 97 mg/dL, and the glucose level was low at 32 mg/dL, while the serum glucose level was within the normal range at 86 mg/dL.

Serological testing for brucellosis (Rose-Bengal, 2-mercaptoethanol (2ME), and Venereal Disease Research Laboratory (VDRL)) were negative for both IgM and IgG antibodies. Wright and Coombs-Wright Brucella antibody titers were only 1/40, an insignificant result for brucellosis. Two sets of blood cultures were also performed, both of which remained negative after seven days. Electrolyte levels, including BUN, creatinine, potassium, calcium, iron, ferritin, and liver enzymes (ALT, AST, ALP), were within normal limits, though sodium levels were mildly low. Red blood cell and platelet counts were also lower than normal, while prothrombin time (PT) and international normalized ratio (INR) were normal, but partial thromboplastin time (PTT) was below normal [Table 1].

Laboratory examination results performed during the patient's hospitalization are shown in Tables 1 and 2.

Abdominal and pelvic ultrasound revealed splenomegaly, with several cystic lesions in the subcapsular region of the right kidney. Computerized tomography (CT) scan results indicated hydrocephalus and meningitis. Magnetic resonance imaging (MRI) of the brain showed multiple ischemic lesions and generalized atrophy. Based on these findings, meningitis and tuberculosis (TB) were considered as possible diagnoses. The patient was initially treated with a combination of antibiotics, including ceftriaxone (500 mg), vancomycin (125 mg), cefepime (500 mg), ampicillin (250 mg), cotrimoxazole (TMP/SMX=160/800 mg), and ciprofloxacin (500 mg) on the seventh day of hospitalization. Rifampin (600 mg) and levofloxacin (500 mg) were administered for suspected TB. Dexamethasone and haloperidol were used to manage symptoms, while sedatives (clonazepam and lorazepam) were given for insomnia and anxiety. The following day, the patient's clinical condition improved, with reduced weakness, lethargy, delirium, and malaise.

By the ninth day of admission, the patient experienced suprapubic pain and abdominal tenderness, followed by signs of phlebitis and edema in the right lower limb. On the 13th day, despite treatment, the patient's weakness and lethargy persisted, and he developed lower limb pain. His vital signs remained stable, and electrolyte levels and blood cell counts were normal. A trace amount of blood was observed in the urine. Abdominal ultrasonography and chest X-ray were normal. On the 15th day of hospitalization, Wright, Coombs-Wright, and 2ME antibody titers against *Brucella melitensis* were 1/160, 1/160, and 1/80, respectively. ELISA testing revealed positive IgM and IgG antibodies against *B. melitensis* in both serum and CSF samples. A standard agglutination test (SAT) titer of 1/320 further supported the diagnosis of brucellosis.

Table 1: The blood cell laboratory results of the patient during admission.

Date	RBC, CMM×10 ³	WBC, CMM×10 ³	Hb, g/L	HCT, %	PLT, CMM×10 ³	PTT, s	PT, s	INR	NEUT, %	LYMP, %
21-07-2022	4.18	4.6	10.6	-	147	-	-	-	9	91
26-07-2022	4.15	7	12.7	-	75	46	-	-	-	-
27-07-2022	4	5.7	12	-	94	-	14.3	1.1	-	-
30-07-2022	3.9	5.8	11.6	33	69	-	14.3	1.1	-	-
31-07-2022	3.92	5.8	11.6	-	69	-	-	-	-	-
01-08-2022	3.95	4.4	12	-	181	-	-	-	-	-
02-08-2022	4	8.7	13	-	190	-	-	-	-	-
03-08-2022	4.12	7.9	11.8	-	189	-	-	-	-	-

Table 2: The blood biochemistry results of the patient during admission.

Date	BUN, mmol/ L	Na, mmol/ L	K, mmol/ L	Cr, mmol/ L	Cu, mmol/ L	Iron, μmol/ L	TIBC, μg/dL	Fer, ng/dL	BS, mg/dL	HbA1c , g/dL	AST, U/L	ALT, U/L	ALP, U/L	TSH, mIU/L
25-07-2022	20	129	3.6	1.3	9	-	-	-	119	-	16	14	102	0.42
27-07-2022	17	127	3	1.2	8	28	373	157	115	4.6	-	-	-	0.42
27-07-2022	15	128	3	1.6	-	-	-	-	109	-	-	-	-	-
28-07-2022	-	128	3.4	-	-	-	-	-	152	-	-	-	-	-
30-07-2022	10	128	3.3	0.9	-	-	-	-	101	-	-	-	-	-
01-08-2022	11	135	3.5	1	-	-	-	-	-	-	-	-	-	-
02-08-2022	12	135	3.5	1.1	-	-	-	-	-	-	27	26	183	-
04-08-2022	14	128	4.7	1.2	-	-	-	-	-	-	30	35	-	-

PCR analysis of the CSF sample definitively identified *B. melitensis* using the following primer pairs, forward: 5'-AAATCGCGTCCCTTGCTGGTCTGA-3' and reverse: 5'-TGCCGATCACTTAAGGGCCTTCAT-3. PCR testing for tuberculosis was negative. Based on these findings, the patient was diagnosed with neurobrucellosis, a rare manifestation of brucellosis affecting the central nervous system.

On the 18th day of hospitalization, the patient was started on a combination antibiotic therapy of cotrimoxazole (TMP/SMX = 160/800 mg, every 12 hours, oral tablet), gentamicin (60 mg, every 8 hours, IV injection), rifampin (600 mg, once a day, oral tablet) and doxycycline (100 mg, every 12 hours, oral tablet), which was continued for two weeks. The patient's condition gradually improved, and he was discharged with medication for three more months. At a seven-month follow-up, the patient had fully recovered with no residual symptoms. Serological and PCR tests were negative, indicating a successful resolution of the infection.

Discussion

Brucellosis remains a significant public health concern in developing countries, particularly in the Middle East and North Africa.^{6,9} While the mortality rate associated with brucellosis is relatively low, morbidity is substantial.^{10,11} In western Iran, specifically Kurdistan Province, brucellosis is an endemic infection. Common routes of human infection include consuming unpasteurized milk and contact with infected animals.^{2,9,12} Given the high proportion of farmers in the population, the prevalence of brucellosis in this region is higher than in other areas.¹³

Brucellosis is a systemic infection that can affect various organs, leading to a diverse range of clinical symptoms, which depend on the infected tissues.¹⁰ The clinical presentation often includes fever, musculoskeletal pain, and sweating. However, the neurological manifestations, particularly in cases of neurobrucellosis (NB), are less common and more challenging to diagnose. Neurobrucellosis affects less than 5% of patients with brucellosis and involves the central and peripheral nervous systems.¹⁴ NB can be associated with a broad range of morbidities, necessitating close monitoring of the patient's neurological condition.¹⁵ The symptoms of NB can mimic other neurological diseases, such as stroke, making diagnosis even more complex.^{9,16,17} Common symptoms include fever, depression, weakness, decreased consciousness, and agitation, which can overlap with other diseases, further contributing to misdiagnosis.¹⁸

In regions where both tuberculosis and brucellosis are endemic, differentiating between neurotuberculosis and NB is particularly challenging. Several scoring systems, such as Thwaites and Lancet, have been developed to aid in the diagnosis of TB meningitis, but these systems can sometimes lead to misdiagnosis when dealing with NB.¹⁵ In our case, initial diagnostic evaluations incorrectly pointed towards neurotuberculosis. This highlights the need for comprehensive assessments involving clinical, laboratory, and imaging findings to avoid misdiagnosis.¹⁰

While cerebrospinal fluid (CSF) cultures are considered the gold standard for diagnosing NB, their sensitivity is relatively low due to the slow growth of *Brucella* species in synthetic media. Only 50% of cases yield positive culture results, and the method is time-consuming. Blood cultures are also less effective due to high costs and potential risks.^{15,19} Imaging studies such as CT scans and MRI scans may provide supportive evidence for NB diagnosis, particularly in cases with tissue damage or complications like meningeal inflammation. However, these methods alone are not sufficient for definitive diagnosis. More reliable diagnostic approaches including molecular techniques, serological tests, and CSF analysis are considerable for correct and definitive diagnosis of NB.¹⁰ CSF analysis can reveal characteristic abnormalities such as normal or decreased glucose levels, increased lymphocyte count, and elevated protein levels. These findings can significantly increase the suspicion of NB and guide further diagnostic investigations.²⁰

Brucellosis infection presents both acute and chronic phases, leading to significant serologic changes, which can result in false negatives in antibody detection tests. Our study recommends employing specific serological methods concurrently with advanced molecular tests such as PCR, medical imaging scans, in addition to blood and CSF cultures for accurate diagnosis of the disease. NB has chronic progression and often exhibits a gradual onset of symptoms and requires long-term treatment with a slow response.²¹ A multi-combination antibiotic therapy based on antibiogram susceptibility testing is crucial for patient recovery. In our case, a prescription of cotrimoxazole, gentamicin, rifampin, and doxycycline demonstrated remarkable efficacy. It is imperative to emphasize the completion of the extended

medication regimen, for six months,²² coupled with continued patient monitoring over subsequent months. This vigilance is fundamental to securing the patient's recovery, particularly given the long-lasting and chronic characteristics often associated with brucellosis.^{23,24}

Given that Kurdistan Province is an endemic region for brucellosis, with neighboring countries like Turkey also reporting high rates of NB, it is essential for clinicians to maintain a high index of suspicion for NB in patients presenting with complex neurological symptoms, especially in high-risk populations.^{2,3,13,21,25} Early and accurate diagnosis, followed by appropriate treatment, is crucial for preventing long-term complications and ensuring a favorable prognosis. This study has limitations, including an inability to generalize, no possibility to establish cause-effect relationships, its retrospective design, and the absence of a comparison group.

Conclusion

The varied clinical manifestations of neurobrucellosis require careful consideration from clinicians, particularly in patients with unexplained and complex neurological complaints in endemic regions like western Iran. Timely and accurate diagnosis necessitates a comprehensive approach that includes a thorough patient history, clinical examination, neuroimaging, and a variety of laboratory tests such as serological assays, molecular methods like PCR, and occasionally blood and CSF cultures. Despite the diagnostic challenges, a high index of suspicion and a methodical diagnostic approach can lead to favorable outcomes for patients with NB.

Disclosure

The authors declared no conflicts of interest. The patient provided written informed consent for the publication of any potentially identifiable data or images involved in the current study.

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