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 shows a challenging case of NB in a 69-year-old man from western Iran. Our 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 disorder, and delusions. Initial workup with cerebrospinal fluid analysis, blood cultures, and serological tests for brucellosis were inconclusive. Neuro-imaging revealed hydrocephalus, meningitis, and multiple ischemic lesions. Initial treatment with broad-spectrum antibiotics and antituberculosis medications for suspected meningitis or tuberculosis had limited effect. 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. According to 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. Our case highlights the diagnostic challenges of NB, mainly 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 against to NB, leading to favorable outcomes.

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

Introduction

Brucellosis as one of the most common zoonotic diseases is widespread among human and animals. Generally, the incidence rate of Brucellosis in Iran has increased in recent years.[1,2] Kurdistan is one of the main provinces in the west of Iran with reports of high incidence of brucellosis annually. Between 1999 and 2008, more than 10,000 cases of brucellosis being reported in this province.[3]

Clinically, brucellosis infections are very extensive, and they are acute, sub-acute or chronic. In various form of infection, multiple organs can be involved.[4,5] Typically, different tissues and organs including gastrointestinal, genitourinary and cardiovascular systems can be involved by brucellosis.[2] Generally, fever, sweating, body pain, splenomegaly, hepatomegaly, and other systemic manifestation are well-known clinical presentations of brucellosis.[4] However, neurobrucellosis (NB; central and peripheral nervous system involvement) is a human threatening and unusual clinical manifestations of brucellosis.[6,7] Neurobrucellosis occurs in 3% to 10% of cases with both central and peripheral nervous system involvement and can be seen in all stages of course infection.[3,4] Although, different signs

were reported as clinical manifestations of NB, meningitis, encephalitis, and meningoencephalitis are known as frequent manifestations.[3,6] Considering that NB can be insidious and appears in several atypical forms, its diagnosis will be delayed. On the other hand, because neurological complications can progress chronically, NB is often misdiagnosed as other diseases such as tuberculosis. NB is usually diagnosed 2 to 12 months after the onset of symptoms.[8]

Here, we presented a case referred with unexplained neurological problems to our hospital and diagnosed NB. Thus, consideration of NB for each patient with unexplained neurological manifestation is critical.

Case Report

A 69-year-old man from Kurdistan province in western Iran with a weight of 71 kg complained of malaise, weakness, lethargy, loss of consciousness, and generalized musculoskeletal pain that had appeared over the past week and intensified over the last two days, was admitted to the Tawheed medical, educational and therapeutic center on July 20, 2022. Additionally, He had been experiencing mild cognitive problems, memory disorders, and delusions for the past two months, during which he also experienced 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 the time of 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) revealed no abnormal findings.

After seven days of hospitalization, the patient developed a headache and muscle pain. During this time, diagnostic procedures and supportive and sedating treatments were undertaken. 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. In contrast, the serum glucose level was within the normal range at 86 mg/dL.

Serological testing for brucellosis using the Rose-Bengal, 2-mercaptoethanol (2ME), and Venereal Disease Research Laboratory (VDRL) methods yielded negative results for both IgM and IgG antibodies. The Wright and Coombs Wright *Brucella* antibody titers were only 1/40, which is considered insignificant in the context of brucellosis diagnosis. Two sets of blood cultures were also performed, both of which remained negative after seven days.

The amounts of electrolytes including BUN, Cr, K, Ca, Iron, Fer, P and liver enzymes including ALT, AST and ALP were within normal limits; however, the rate of Sodium (Na) was mildly lower than the normal rate. The rate of RBC and platelets were lower than the normal range. Although the level of PT and INR was normal, the rate of PTT was lower than the normal range (**Table 1**). Laboratory examination results performed during the patient's hospitalization are shown in the **Tables 1** and **2**.

Table 1. The blood cells 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	-	-

The abdominal and pelvic ultrasound revealed splenomegaly, accompanied by several cystic lesions containing fluid in the subcapsular region of the right kidney. Additionally, the results of the computerized tomography (CT) scan indicated the presence of hydrocephalus and meningitis. Furthermore, the magnetic resonance imaging (MRI) of the patient's brain displayed multiple ischemic lesions and generalized atrophy. Based on these findings, the differential diagnosis was narrowed down to meningitis and tuberculosis (TB).

According to the initially diagnosis, the patient was 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 also administered as part of the treatment regimen for TB. Dexamethasone and antipsychotic haloperidol were prescribed to manage the patient's symptoms, and sedatives including clonazepam and lorazepam were used to alleviate insomnia and anxiety. The following day, the patient's clinical condition showed improvement, with reduced symptoms of weakness, lethargy, delirium, and malaise.

On the ninth day of admission, the patient complained of pain in the suprapubic area and developed abdominal pain. This area was slightly stiff and tender during the examination. On the 13th day of hospitalization, signs of phlebitis of the right lower limb and edema (+1) were observed. Although the treatment was given to the patient, his complaints such as weakness and lethargy continued, and lower limbs pain was added to the patient. The vital signs of the body were stable and the level of electrolytes and blood cell count was 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* (*B. melitensis*) species were 1/160, 1/160 and 1/80, respectively. To further confirm the diagnosis, enzyme-linked immunosorbent assay (ELISA) was employed, revealing positive IgM and IgG antibodies against *B. melitensis* in both serum and CSF specimens. Additionally, a positive standard agglutination test (SAT) at a titer of 1/320 on the patient's serum sample further supported the diagnosis of brucellosis.

Polymerase chain reaction (PCR) analysis of CSF sample definitively identified *B. melitensis* by the following specific primer pairs, forward: 5′-AAATCGCGTCCTTGCTGGTCTGA-3′ and reverse: 5′-TGCCGATCACTTAAGGGCCTTCAT-3. PCR testing for tuberculosis, on the other hand, yielded negative results. Based on these diagnostic findings, the patient's condition was ultimately diagnosed as neurobrucellosis, an uncommon manifestation of brucellosis affecting the central nervous system. On the 18th day of hospitalization, a combination antibiotic therapy involving 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) was initiated. This regimen was continued for two weeks, and the patient's clinical condition gradually improved. Following discharge from the hospital, the patient continued the specific prescribed medication for an additional three months. After a seven-month follow-up period, the patient had fully recovered, with no residual symptoms or signs of NB. Laboratory tests, including serological assays and PCR, also returned negative results, 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, the morbidity rate is substantial.[10,11] In western Iran, specifically Kurdistan Province, brucellosis is a prevalent endemic infection. Several routes of human infection are recognized, but consumption of unpasteurized milk and conventional cheese prepared using unheated methods are considered the primary sources. Occupational exposure through direct contact with infected animals is another significant risk factor for brucellosis.[2,9,12] As farmers form a substantial portion of the population in this region, they are at an elevated risk of contracting the disease.[13] This explains the higher prevalence of brucellosis in this region compared to other areas.

Brucellosis is a systemic infection that can affect various organs, resulting in a diverse range of clinical symptoms that depend on the affected tissues and organs.[10] The clinical presentation of brucellosis exhibits variability, often characterized by fever, musculoskeletal pain, and sweating symptoms. However, its atypical neurological manifestations make diagnosis challenging, with direct nervous system involvement occurring in fewer than 5% of patients with brucellosis.[14] Neurobrucellosis (NB) is a complex and severe form of brucellosis that involves both the central and peripheral nervous systems (4). NB may be linked to a broad range of morbidities, necessitating vigilant monitoring of the patient's neurological condition.[15] The clinical manifestations of NB can mimic those of other peripheral and central nervous system diseases as well as stroke.[9,16,17] Common symptoms include fever, depression, weakness, decreased consciousness, and agitation. This overlap in symptoms can lead to misdiagnosis.[18] In regions endemic to tuberculosis and brucellosis, distinguishing between neurotuberculosis and NB poses a significant challenge due to the similarity of clinical symptoms. Various criteria, including the Thwaites and Lancet scoring systems, have been developed to facilitate the swift diagnosis of TB meningitis.[15] However, this study observed a misdiagnosis of NB as neurotuberculosis based on initial assessments. Therefore, a comprehensive evaluation involving clinical findings and laboratory tests is essential for accurate diagnosis.[10] While culture of cerebrospinal fluid (CSF) on appropriate microbiological media is considered the gold standard for NB diagnosis, its sensitivity is relatively low due to the slow growth of *Brucella* species in synthetic media (only 50% of cases are positive) and the time-consuming nature of the method. Blood culture, on the other hand, is considered less suitable due to its potential risks and high cost, and its results may also be negative.[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 a 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].

Kurdistan is considered as one of the most important endemic provinces for brucellosis infection in the west of Iran, where various types of the disease, including NB, have been reported.[2,3,13] A numerous cases of NB have been reported in neighboring countries in the west of Iran, such as Turkey, which are considered endemic areas of infection.[13,21,25] Therefore, suspicion of NB in patients with complex neurological symptoms, especially in high-risk populations in these regions, is crucial for timely diagnosis and appropriate treatment.

In conclusion, the varied clinical manifestations of NB necessitate careful consideration by physicians for early diagnosis of NB. It seems reasonable to consider NB in patients with uncertain neurological etiology, who present with unexplained and complex neurological complaints, particularly in endemic regions like the west of Iran. Timely and accurate diagnosis and treatment require a comprehensive approach, including patient history, clinical examination, neuro-imaging scans and laboratory tests such as a variety of serological tests, molecular methods, alongside occasionally blood and CSF samples cultures.

This case-report 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.

Disclosure

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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