Neurobrucellosis: A differential not to be missed in patients presenting with neuropsychiatric features

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Abstract
When a patient presents with undulating fever and neuropsychiatric features, neurobrucellosis should be considered as a differential diagnosis. If diagnosed early, neurobrucellosis is a treatable disease with a favorable outcome.

KEYWORDS
brucella, catatonia, neurobrucellosis, serology

1 | INTRODUCTION

Brucellosis, caused by the bacterium Brucella, is one of the most important zoonotic diseases affecting livestock and humans all over the world. Brucella is a small aerobic intracellular coccobacilli located in the urogenital tract of the host animal, causing abortion and infertility. Brucellosis is usually caused by Brucella abortus in cattle, B. melitensis in sheep/goats, B. suis in pigs, and B. canis in dogs. They are shed in large numbers in the animal's urine, milk, placental fluid, and blood.1,2 Brucellosis is transmitted to humans through unpasteurized milk, occupational contact with infected animals, and animal products.3

Human brucellosis is a multisystem disease that may present with a broad spectrum of clinical manifestations and complications.2,4 It can be classified as acute (septicemia), subacute (secondary localization), and chronic (>1 year) brucellosis.2 Neurobrucellosis may develop at any stage of disease and have heterogeneous manifestations, including encephalitis, meningoencephalitis, radiculopathy, myelitis, peripheral and cranial neuropathies, cerebral venous thrombosis, subarachnoid hemorrhage, and psychiatric manifestations.5,5

Evidence regarding brucellosis in Nepal is lacking. Most of the publications have focused on bovine brucellosis with sparse information available on human brucellosis. In Nepal, brucellosis is a serious public health threat posed by endemic bovine and goat brucellosis. An animal study conducted in Nepal showed that the overall brucellosis seroprevalence rate was 12%.6 The first human case was reported in 1979 when the disease was diagnosed by the isolation of brucella from a shepherd in Pokhara.7 Thereafter, few data have been published, most of which are limited to gray literature. Pyakurel et al in 1980 found that the prevalence of Brucella abortus agglutinins in Nepalese serum ranged from 2% in urban residents to 5% in remote mountainous residents.8 Joshi et al in 1984 found that among 2117 residents of Kathmandu city, the seroprevalence of brucella was 2.7%.9 Since then, there has been no new evidence of brucellosis in Nepal. Besides, no paper has been published from Nepal on neurobrucellosis. Therefore, we herein, report a case of a 20-year-old Nepalese female with Neurobrucellosis and discuss the relevant literature.
2 | CASE REPORT

A 20-year-old female housewife, a resident of southern Nepal, presented to the emergency room of Tribhuvan University Teaching Hospital with insidious onset of altered behavior, irrelevant talks, excessive crying, and increased reticency for 45 days. She also experienced undulating fever for the same duration. Her caretakers gave an undocumented history of psychiatrist consultation at about the 30th day of her symptoms, following which there was mild improvement in her symptoms. However, after a week, the patient again developed altered sensorium with high-grade fever, and temperature recorded maximum of 103 Fahrenheit. The fever was not associated with chills or rigors. However, it was associated with malaise, weakness, anorexia, headache, myalgia, and back pain. There was no history of headache, nausea, vomiting, neck stiffness, photophobia, blurred vision, motor weakness, abnormal movements, gait problem, sensory loss, seizure, syncope, tremors, malignancy, rheumatological disease, and exposure to toxic substances. The patient had no cough, hemoptysis, night sweats, and weight loss. The patient has a mixed diet habit and did not drink alcohol and smoked a cigarette in her lifetime. There was no history of drug abuse or any medication intake. Her medical, surgical, and psychiatric history was unremarkable. She had no distant or recent mental trauma. Her family history was unremarkable. She is a housewife and farmer, involved in agriculture and animal husbandry. She gave no recent history of pesticide or insecticide or fumigant use. She rear cattle in her home, including 5 cows and two buffalos, with no pigsty.

On examination, her blood pressure was 160/100 mm Hg, pulse rate of 88 beats per minute, temperature of 39°C, and respiratory rate of 20 breaths per minute. Her oxygen saturation (SpO2) was 96% in room air as measured by the pulse oximeter. There was no pallor, icterus, lymphadenopathy, edema, cyanosis, or clubbing. The cardiac examination revealed normal S1 and S2 without murmur. On auscultation of the chest, bilateral normal vesicular breath sound was heard with no added sounds. Per abdominal examination revealed no pelvic mass and organomegaly. Central nervous system examination revealed mutism. There were no cranial nerve abnormalities. Motor examination showed normal muscle bulk, normal reflexes, bradykinesia, and generalized rigidity. A sensory and cerebellar examination could not be assessed. Examination of other systems did not reveal any abnormalities.

Hemogram, renal function test, thyroid function test, and liver function test were normal. Sputum microscopy was negative for the acid-fast organism, so was GeneXpert PCR. The serological examination was negative for antinuclear antibodies (ANA), anti-double-stranded DNA antibodies (anti-dsDNA), rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP), and anti-neutrophil cytoplasmic antibodies (ANCA). Inflammatory markers including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were raised.

A tropical panel including those for scrub typhus, leptospirosis, leishmaniasis, malaria was normal. However, spot brucella antibody was positive, following which ELISA was done which confirmed the presence of brucella antibody. Blood culture for brucella culture was then sent, which later came out to be negative. Cerebrospinal fluid (CSF) analysis showed normal color, lymphocytic pleocytosis, low glucose, and elevated protein and adenosine deaminase (ADA) level. CSF microscopy on gram staining and acid-fast staining showed no organism. CSF GeneXpert PCR for mycobacterium was negative. However, the CSF ELISA test showed a positive brucella antibody. CSF culture for brucella was negative. Abdominal/pelvic ultrasound, chest X-ray, X-ray lumbar-sacral spine, MRI brain, and CNS venogram were normal. The electroencephalogram was also normal. Owing to the brucella seropositivity and CSF antibody positivity, history of cattle rearing, clinical features compatible with neurobrucellosis, clinical improvement after starting appropriate treatment, and inability to prove a more suitable alternative diagnosis, the diagnosis of Neurobrucellosis was made.

During the time of hospital stay, the patient was treated in the line of Neurobrucellosis. Intravenous antibiotics (ceftriaxone, rifampicin, and doxycycline), lorazepam, and olanzapine were administered. The patient developed no complications during her stay. The patient was discharged after 4 weeks when there was significant regression of symptoms, patient self-mobilization, and dual communication. The patient was advised to follow-up after 2 months or whenever necessary and to continue supportive care, physiotherapy, and psychiatric consultation. At discharge, she was advised to continue rifampicin and doxycycline, lorazepam, and olanzapine. At two months follow-up, she is doing well, with no residual neurological and psychiatric manifestations.

3 | DISCUSSION

We embarked on what is, to our knowledge, the first reported case of Neurobrucellosis from Nepal. Our patient, a 20-year-old female, presented with undulating fever and insidious onset altered behavior, irrelevant talks, excessive crying, increased reticency for one and half months. Clinical features, laboratory investigations, and radiological findings all pointed toward a diagnosis of Neurobrucellosis. Although the diagnosis of Neurobrucellosis can be made based on classic clinical, radiological features, serological and tropical panels, it is often under-diagnosed due to the lack of qualified health workers and limited resources in the context of Nepal. Furthermore, the lack of clinical and epidemiological studies related to Neurobrucellosis in Nepal makes clinicians unaware of this condition, leading to misdiagnosis.
Fulfilling any of the following criteria will be sufficient to diagnose Neurobrucellosis:

- Symptoms and signs consistent with neurobrucellosis.
- Bacteria isolation from blood and other body fluids.
- Antibody positivity; titer >1/160 in serum, and >1/80 in CSF, or weekly antibody titer increase.
- CSF findings, revealing chronic meningitis (lymphocytic pleocytosis, increased protein level, decreased glucose level).
- Diagnostic findings in brain computed tomography or MRI.

Our patient qualified three different criteria to diagnose Neurobrucellosis. Furthermore, clinical improvement after starting an appropriate treatment made our diagnosis more robust.

Neuroimaging findings in neurobrucellosis are highly heterogeneous. A large scale study from Turkey showed that neuroimaging in neurobrucellosis can be classified into various groups as follows:

- **Group 1:** Normal.
- **Group 2:** Inflammatory changes.
  - a. Diffuse inflammation: Leptomeningeal involvement, basal meningeal enhancement.
  - b. Localized inflammation: Cranial nerve involvement, spinal nerve root enhancement, brain abscess, granuloma, and arachnoiditis.
- **Group 3:** White-matter abnormalities/demyelinating lesions.
- **Group 4:** Vascular insults: Chronic cerebral ischemic changes, acute cerebral ischemia, subdural hematomas, and subarachnoid hemorrhage.
- **Group 5:** Cerebral edema/Hydrocephalus.

Although rare, apart from the aforementioned findings, deep gray matter involvement has also been documented in the literature. The reasons for such variable manifestations in neurobrucellosis remain obscure. As in our case, even if the patient has normal neuroimaging, the diagnosis should not be excluded.

When a 20-year-old female presents an insidious onset of psychiatric manifestation with febrile illness, numerous differentials emerge, apparently important to rule out. In our country, the most important differential diagnosis of this presentation is CNS tuberculosis.

Neurobrucellosis and CNS tuberculosis, both chronic granulomatous infectious diseases, are endemic in our country, and there is a significant imbrication of clinical characteristics, the CSF study, and neuroimaging among the aforementioned diseases. However, sputum and CSF microscopy along with the PCR test can help rule out tuberculosis. Similarly, schizophrenia and affective disorders may be other common differentials. However, if a detailed history is taken, these psychiatric illnesses can be easily ruled out. The prevalence of HIV infection among adults in Nepal is around 0.20%. Therefore, CNS toxoplasmosis should be considered an important cause. Brain CT in cerebral toxoplasmosis appears as multiple hypodense lesions predominantly in the basal ganglia and the corticomedullary junction, with perilesional edema, and after contrast administration, there is ring enhancement. The T2 MRI sequence shows hyperintensity in necrotizing abscesses and isointensity in organized abscesses of CNS toxoplasmosis. An alternating concentric zone of hypo/hyper/isointense signal known as a concentric target sign is also seen on T2 MRI. Anti-NMDAR encephalitis is another important differential in a young woman with neuropsychiatric symptoms. However, it is of acute or subacute onset and occurs in association with ovarian teratoma. In this condition, MRI shows T2 hyperintensities in the hippocampus, frontal lobe, cingulate gyrus, corpus callosum, insula, basal ganglia, thalamus, and brain stem. EEG shows delta range slowing, delta brush, generalized rhythmic delta activity, epileptiform discharges, etc.

Although rare, old infarction, normal pressure hydrocephalus, subdural hematoma, mitochondrial encephalomyopathy, CNS vasculitis, postinfectious demyelination, and CNS malignancy, neurosarcoïdosis, multiple sclerosis, early-onset Alzheimer’s disease, early-onset Parkinson’s disease, and Creutzfeldt-Jakob disease can also have a similar presentation. However, a detailed history, clinical examination, and neuroimaging can effectively rule out the aforementioned diseases. Toxic metabolic causes (such as renal failure/uremia and liver failure) systemic diseases (such as thyroid and adrenal diseases), vitamin deficiencies (such as cyanocobalamin, niacin), porphyria and heavy metal poisoning, and systemic lupus erythematosus can also produce subacute/chronic neuropsychiatric symptoms, as seen in our patients. However, metabolic, biochemical, and rheumatological studies can help rule out these systemic diseases.

Neurobrucellosis is a treatable disease with a good prognosis. Doxycycline, rifampicin, and third-generation cephalosporins for at least 6 weeks are considered the standard drugs and first-line drugs for neurobrucellosis. Our patient was treated with ceftriaxone, rifampicin, doxycycline, lorazepam, and olanzapine, and the symptoms resolved significantly at 2 months follow-up. The prognosis of neurobrucellosis varies according to clinical manifestations. The prognosis of the meningitis group is usually better. However, in encephalitic or spinal cord involvement, mortality and neurological sequelae are more common. Despite appropriate antibiotic treatment, neurological sequelae such as aphasia, hearing loss, and hemiplegia have been reported among survivors.
CONCLUSIONS

The neuropsychiatric manifestations of neurobrucellosis can be confused with CNS tuberculosis, schizophrenia, affective disorders, CNS toxoplasmosis, and anti-NMDAR encephalitis. When the patient presents with undulating fever and neuropsychiatric features, neurobrucellosis should be considered as a differential diagnosis.

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CONFLICT OF INTEREST

The authors declare no conflict of interests in association with this manuscript.

AUTHOR CONTRIBUTIONS

GN, RB, SB, SA, and RO: reviewed the literature and designed the manuscript. RO, BPG, RK, RR, GN, SP, NG, and AS: established the diagnosis and treated the patient. All authors read and approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

There is no need for ethical approval for a case report according to the local ethical guideline. Written informed consent was taken from the patient in the Nepali language to include her clinical details in this article.

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