

Case Report

Neurobrucellosis: a case report

Supriya Patil, Meenakshi G. Narkhede*

Department of Medicine, S. B. H. Govt. Medical College, Dhule, Maharashtra, India

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***Correspondence:**

Dr. Meenakshi G. Narkhede,

E-mail: Meenakshinarkhede@hotmail.com

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ABSTRACT

Neurologic involvement of brucellosis is common but exact prevalence of it is unknown due to difficulty in diagnosis and inadequate reporting all over the world. Neurologic involvement may manifest as chronic meningitis, lymphocytic meningoencephalitis, a variety of cranial nerve deficits, or ruptured mycotic aneurysms. We report a case of young male who had history of fever and headache on and off for 2 years and later developed signs of meningitis, lateral rectus palsy, altered sensorium and bilateral papilledema. He did not respond to anti-tubercular therapy and antibiotics. CT scan and MRI brain were normal. He had hepato-splenomegaly with small hypoechoic lesions in the spleen. CSF culture grew gram negative bacilli. Brucella IgG antibodies in serum by EIA 7, IgM negative, Brucella antigen titer was positive, 1:160. Patient received inj. streptomycin 0.75 g for 21 days and doxycycline 100 mg twice daily doxycycline for 6 weeks. The complete improvement in patient's condition after a long lasting illness motivated authors to report this case. Delay or failure in diagnosis of this treatable disease may lead to significant morbidity and mortality so high index of suspicion should be kept in such cases.

Keywords: Neurobrucellosis, Meningoencephalitis

INTRODUCTION

Brucellosis is an important multisystem zoonotic disease in India, but it is often underdiagnosed due to lack of suspicion and diagnostic facilities. Brucellosis is endemic in many countries especially in rural areas and India is not an exception. This zoonotic disease is present in all livestock systems. Increased demand for dairy products, changing and intensified farming practices has raised the concern for increased spread and intensified transmission of this infection to human population.¹

Brucella is gram-negative, nonmotile, facultatively intracellular coccobacilli that can replicate inside mononuclear phagocytes. To date, 8 species have been identified, named primarily for the source animal or features of infection. Of these, 4 have moderate-to-significant human pathogenicity: i) *Brucella melitensis* (from sheep; highest pathogenicity) ii) *Brucella suis* (from

pigs; high pathogenicity) iii) *Brucella abortus* (from cattle; moderate pathogenicity) iv) *Brucella canis* (from dogs; moderate pathogenicity). After ingestion of infected products, hematogenous dissemination occurs, followed by residence in the reticulo-endothelial system and resultant involvement of any organ. The spectrum of systemic involvement includes hematologic, gastrointestinal, cardiorespiratory, and musculoskeletal systems.² Neurologic manifestations of brucellosis occur in 0%-25% of patients.³

Different routes of transmission include contaminated unpasteurized milk, ingestion of raw meat and offal may be the main source of infection. Occupational exposure to persons working with animal's farm, laboratory personnel handling culture media of *Brucella* can get infected.

Transmission person to person is extremely rare, have been reported occasionally through blood transfusion, and organ transplantation. There is evidence of breast milk and sexual transmission. Inhalation of contaminated dust, drinking water may cause infection.⁴

Brucellosis may cause different clinical neurological syndromes like acute toxic manifestations, meningitis, diffuse or localized encephalitis, myelitis, radiculitis, neuritis, multiple cerebral or cerebellar abscesses, ruptured mycotic aneurysm and subarachnoid hemorrhage. Guillain - Barre syndrome, cranial nerve palsies, hemiplegia, sciatica, myositis, and rhabdomyolysis. Papillitis, papilledema, retrobulbar neuritis, optic atrophy and ophthalmoplegia due to lesion in cranial nerve III, IV, VI may occur in brucella meningoencephalitis. The most common neurologic manifestation is a subacute or chronic meningoencephalitis. Many other CNS manifestations of neurobrucellosis have been reported: arachnoiditis, cerebellar syndromes, ruptured basilar aneurism, hemiparkinsonism, chorea, anterior poliomyelitis. Acute toxic manifestations of disease are seen during the acute phase of infection, and include headache, neckache, backache, insomnia, depression and muscle weakness. Motor manifestations occur frequently and generally present in the form of paresis of variable intensity, with gait disturbances. Sensory symptoms usually consist of paraesthesias and occasionally gait apraxia. Cranial nerves involvement, generally the sixth, seventh, and eight is relatively frequent findings. The involvement of the eight cranial nerve is reported a very characteristic of the brucellar meningitis. All this diverse manifestations can lead to confusion and delay in diagnosis. It may also lead to difficulty in differentiating neurobrucellosis from other chronic infections, especially tuberculosis and syphilis.⁵

The clinical spectrum of neurobrucellosis may be classified as central and peripheral and acute or chronic in terms of duration. It may present clinically as meningitis, meningoencephalitis, meningovascular involvement, parenchymatous dysfunction, peripheral neuropathy, radiculopathy, and various degrees of behavioral abnormalities. Meningitis has been the most frequent presentation in various clinical case reports. Central nervous system involvement occurs in less than 5% of patients, the majority being around 2%–5%. The effect on nervous system can be due to direct effect of bacilli, cytokines or endotoxins on peripheral nerves, spinal cord, meninges and brain. The involvement can also be secondary to the bone disease caused by brucella or abscess formation in the brain. Nervous system can be involved in various stages of brucellosis i.e. at the onset of illness, during the course of illness or during convalescence or months after recovery from acute infection.⁶

The criteria necessary for definite diagnosis of neurobrucellosis are 1) neurological dysfunction not

explained by other neurologic diseases, 2) abnormal CSF indicating lymphocytic pleocytosis and increased protein, 3) positive CSF culture for Brucella organisms or positive Brucella IgG agglutination titre in the blood and 4) CSF response to specific chemotherapy with a significant drop in the CSF lymphocyte count and protein concentration. Our patient fulfilled all the above mentioned criteria for the diagnosis of neurobrucellosis except that the CSF IgG agglutination titre was not significantly high. Demonstration of Brucella organism from CSF in culture media is the confirmatory test for diagnosis of neurobrucellosis. However, this is uncommon in most of the series and yield does not exceed 30%. STA test may give false negative titre because of the blocking antibodies.⁷

Brucella infection is primarily controlled through cell-mediated immunity rather than antibody activity, some immunity to reinfection is provided by serum immunoglobulin (Ig). Initially, IgM levels rise, followed by IgG titers. IgM may remain in the serum in low levels for several months, whereas IgG eventually declines. Persistently elevated IgG titers or second rises in IgG usually indicate chronic or relapsed infection. IgA antibodies are elaborated late and also may persist for very long intervals.⁸

CASE REPORT

A young male, 24 years old who was admitted in April 2013 in our institution with mild to moderate grade fever without chills and rigors on and off, generalized weakness since two years, headache and diplopia since 8 months. He got admitted in this hospital with fever, irritability and altered sensorium since last 6 days. There was no history of vomiting or convulsions. There was no history of milking cows and goats daily and also consumption of raw milk. He was treated for malarial fever, enteric fever and was also started on anti tuberculous treatment which he stopped after 5 months on his own as there was no relief. On examination, he was febrile had 100⁰ F temperature, pulse was 108/min, regular, blood pressure 110/70 mmHg, and respiratory rate 20/ min. He was anaemic and had no icterus, clubbing, lymphadenopathy. He had mid hepatosplenomegaly.

On neurological examination he was irritable and confused. He had neck rigidity, positive Kernig's sign, right lateral rectus palsy and nystagmus. Pupils were equal and reacting to light. Fundus examination showed bilateral papilledema. Cardiovascular and respiratory system were unremarkable. Blood examination revealed haemoglobin of 9.5 gm%, white cell counts 4500/mm with normal differential count and ESR of 37 mm at the end of 1hour. Other investigations including renal and liver function tests were within normal limits. Peripheral blood film for malarial parasite was negative. Widal test was negative. Blood culture examination did not grow any organism. Chest X-ray was normal. USG abdomen

and pelvis showed mild hepatosplenomegaly and small hypoechoic lesions in the spleen suggestive of micro abscesses.

CT scan and MRI brain were normal. VDRL, HIV were negative. Tuberculosis antibody profile TB IgG & IgM were negative. CSF examination showed CSF proteins 90 mg%, sugar 15 mg%, total nucleated cells 520 cmm³ with 90% lymphocytes. CSF culture grew gram negative bacilli. Brucella IgG antibodies, serum by EIA was strongly positive (titre 7, positive >1.1). Standard plate agglutination test for brucellosis in serum was strongly positive with antibody titres of >1:160. Patient was given Inj. Streptomycin 0.75gm daily for 21 days and doxycycline 100mg two times a day for six weeks⁹. He started recovering and became fully conscious in 10 days. Repeat CSF after 6 weeks showed Proteins 68, sugar 23, total cells 140/mm³, Serum antibody titers were less than 1:80 four weeks after starting treatment and CSF titers were less than 1:40 after eight weeks. There were no neurological sequelae on follow-up visit after one month.

DISCUSSION

On review of literature we found few case reports and case series of neurobrucellosis. In the report by al Deeb et al. categorized neurological involvement in brucellosis into 5 groups: acute meningoencephalitis, meningovascular involvement, central nervous system demyelination, peripheral neuropathy, and papilledema and increased intracranial pressure.

Sometimes neurological symptoms may be the only symptoms. The criteria for definite diagnosis of neurobrucellosis are 1-neurological dysfunction not explained by other neurological diseases, 2-abnormal CSF indicating lymphocytic pleocytosis and increased protein, 3-positive CSF culture for Brucella organisms or positive Brucella IgG agglutination titer in the blood and 4-CSF, response to specific chemotherapy with a significant drop in the CSF lymphocyte count and protein concentration.¹⁰

In a pulled analysis of 187 cases of neurobrucellosis done by Gul HC, Erdem H et al. in Turkey. Headache, fever, sweating, weight loss, and back pain were the predominant symptoms, while meningeal irritation, confusion, hepatomegaly, hypoesthesia, and splenomegaly were the most frequent findings. The major complications in patients were cranial nerve involvement, polyneuropathy/radiculopathy, depression, paraplegia, stroke, and abscess formation. Antibiotics were used in different combinations and over different intervals. The duration of antibiotic therapy reported ranged from 2 to 15 months (median 5 months). The mortality was 0.5% with suitable antibiotics. They concluded that Neurobrucellosis may mimic various pathologies so a thorough evaluation of the patient with probable disease is crucial for an accurate diagnosis and proper management of the disease.¹¹

In a study of clinical and neuroimaging correlation of neurobrucellosis done by M. Walid Al-Sousa, Saeed Bohlegaa in Saudi Arabia, they investigated patterns of nervous system involvement and determined if neuroimaging abnormalities correlated with clinical manifestations of neurobrucellosis. They reviewed 23 MR imaging studies (17 of brain, six of spine) and seven CT scans of brain in 23 patients (14 male and nine female patients; age range 17-71 years) with positive Brucella titers in their serum and CSF. Twelve patients had central nervous system (CNS) involvement, four had peripheral nervous system (PNS) involvement, two had combined PNS and CNS involvement, and five had isolated hearing loss. Imaging findings were divided into four types-normal, inflammation (abnormal enhancement), white matter changes, and vascular changes to correlate radiologic findings with clinical manifestation. Imaging findings were variable: five of seven brain CT studies were normal, and 10 of 23 MR studies were normal (eight brain, one thoracic, one lumbar). One brain CT showed subthalamic hemorrhage, mild perivascular enhancement, left caudate lacunae, and diffuse white matter changes. One other brain CT showed enhancement of the tentorium in addition to white matter changes. Abnormal MR findings were basal meningeal enhancement (n = 3), lumbar nerve root enhancement (n = 3), granuloma of the suprasellar region (n = 1), diffuse white matter changes (n = 7), and spinal cord atrophy (n = 1). All patients improved after treatment with three antimicrobial drugs for 3-12 months. Seven patients had follow-up imaging; the enhancement disappeared but the white matter and ischemic changes persisted despite almost complete clinical recovery.¹²

They concluded that clinical-radiologic correlation in neurobrucellosis varies from a normal imaging study, despite positive clinical findings, to different imaging abnormalities.

Awareness of the condition and performance of the appropriate serological tests will differentiate neurobrucellosis from other chronic CNS infections, especially tuberculosis and neurosyphilis.

In one study, three cases of neurobrucellosis were reported by Deniz Tuncel, Hasan Uçmak et al. in Turkey. One patient had diffuse cerebral white matter lesions as leukoencephalopathy who had presented with gait disturbance, behaviour change and seizure. Another patient had bilateral progressive motor weakness for four months and headache for one year. Third patient had left brachio cephalic transient numbness attacks and headache for twenty days. He had signs of meningitis.¹³

Four cases of neurobrucellosis have been reported from Bikaner India by Kochar D K, Kumawat B L et al. presenting as meningoencephalitis one of which also had peripheral neuropathy resulting in delayed nerve conduction velocity. Diagnosis was confirmed by serological test and agglutination titre was >1:320 in all

the patients. All these patients had close contact with animals and history of raw milk ingestion was present in 3 cases. Patients were treated with doxycycline 100 mg twice daily, rifampicin 450 mg twice daily, both orally for eight weeks and streptomycin one gram per day for initial fourteen days as a common therapeutic regimen. No patient had neurological sequelae at the end of the treatment.¹⁴

A single case was reported by Ghosh D, Gupta P, Prabhakar S from Chandigarh. A young adult presenting with 11 months history of fever, headache, vomiting was found to have CSF lymphocytic pleocytosis with increased protein. His serum tested strongly positive for *Brucella* (standard tube agglutination titre 1: 320) whereas CSF was weakly positive. He became asymptomatic on treatment with tetracycline, rifampicin and streptomycin with significant CSF response.¹⁵

In a study done by Meltem Arzu Yetkin, Cemal Bulut et al, they described their experience in the diagnosis, treatment, and the final outcomes of 20 patients with neurobrucellosis out of 305 patients having brucellosis, in a five-year period between January 1999 and June 2004. The rate of neurobrucellosis was 6.6%. Twelve males and eight females with a mean age of 37.4 years were investigated. Fever, headache, confusion, and gait disorders were the main complaints. The duration of their complaints varied between one week and six months. On physical examination, 13 patients had fever, six had neck stiffness and confusion, three had motor deficit on either their upper or lower extremities, and four of them had diplopia. The Rose-Bengal test and standard tube agglutination tests were positive in all of the patients. *Brucella melitensis* was isolated from the blood of six of the 20 (30%) patients. Cerebrospinal fluid (CSF) was analyzed in 18 patients. Pleocytosis with a mean value of 244×10^6 cells/L, and high protein levels were detected in all. A low glucose level in the CSF was detected in ten patients. Patients were treated medically and a complete resolution was achieved in all.¹⁶

In a review of 17 cases of neurobrucellosis done by Hasan Karsen, Suda Tekin Koruk et al. clinical features, cultures, serological tests, additional laboratory findings, and CSF analyses were recorded for all patients. There were 14 female and 3 male patients. Ten patients presented with neuropsychiatric symptoms and signs (aphasia, diplopia, hemiparesis, facial paralysis, tremor, ataxia, depression, personality disorder, and hallucinations). Serum standard agglutination test (SAT) was negative in 4 (23.5%) patients and serum Coombs' test was negative in 2 (11.7%). CSF SAT was negative in 4 (23.5%) patients and CSF Coombs was negative in 3 (17.6%) patients. *B. melitensis* grew in the blood of 6 (35.2%) patients and in the CSF of 3 (17.6%). Treatment protocol for 11 patients consisted of ceftriaxone, rifampicin, and doxycycline for a period of four weeks, followed by rifampicin and doxycycline for an additional four weeks. The remaining patients were given different

treatment combinations. One patient died, mild sequelae was present in another patient and the remaining patients recovered without any sequelae. They concluded that neurobrucellosis should be considered in the differential diagnosis of neurological and psychiatric cases that are encountered in endemic areas for brucellosis. In order to prevent overlooking this diagnosis, Coombs' test should be performed in both CSF and serum.¹⁷

11 cases of neurobrucellosis have been reported by Gul HC, Erdem H, Gorenec L et al. from Turkey. Patients with neurobrucellosis were evaluated. The diagnosis was established by the isolation of bacteria, abnormal CSF findings and positive serology. None of their patients died. Imaging techniques did not provide any specific contribution regarding the *Brucella* infection.¹⁸

A single case of neurobrucellosis presenting as isolated intracranial hypertension has been reported by Sanem Yilmaz, Gul Serdaroglu, and Sarenur Gokben from Turkey. They have reported a case of 15-year-old girl with history of headache and vomiting for 1 month and diplopia for 1 week who had inward deviation of the left eye, bilateral limited outward movement of the eyes, and papilledema. The opening cerebrospinal fluid pressure was 340 mm/H₂O. Serum and cerebrospinal fluid Rose Bengal tests were positive. Wright test was positive at 1/80 titer in cerebrospinal fluid and at 1/160 titer in serum. *Brucella melitensis* was grown on cerebrospinal fluid culture. The case was diagnosed as neurobrucellosis and was treated with triple antibiotic therapy of streptomycin, doxycycline, and rifampicin. The clinical findings and the papilledema had regressed rapidly.¹⁹

Esra Özkavukcu, Zeynep Tuncay, Ferda Selçuk, İlhan Erden, reported an unusual clinical and magnetic resonance imaging (MRI) findings in a patient with neurobrucellosis and unilateral abducens nerve palsy. Her MRI showed punctate leptomeningeal enhancement of the cerebellum on contrast-enhanced T₁-weighted images, and a focal area of hyperintensity in the splenium of the corpus callosum on T₂-weighted images. After treatment and 3 months follow up patient recovered and MRI brain was normal.²⁰

There are many more such case reports all over the world suggestive of difficulty in diagnosis of this disease and complete recovery of patients on treatment. On extensive search of literature we could not find long term follow up of reported cases. As found in the reference book "Harrison's textbook of Medicine, relapse occurs in up to 30% of poorly compliant patients and thus patients should ideally be followed clinically for up to 2 years to detect relapse, which responds to a prolonged course of the same therapy used originally. The general well-being and the body weight of the patient are more useful guides than serology to lack of relapse. IgG antibody levels detected by the SAT and its variants can remain in the diagnostic range for >2 years after successful treatment. Complement fixation titers usually fall to normal within 1

year of cure. Immunity is not solid; patients can be reinfected after repeated exposures. Less than 1% of patients die of brucellosis. When the outcome is fatal, death is usually a consequence of cardiac involvement; more rarely, it results from severe neurologic disease. Despite the low mortality rate, recovery from brucellosis is slow, and the illness can cause prolonged inactivity, with domestic and economic consequences.⁹

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