# Neurobrucellosis
## *Brief Review*

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**Background:** Brucella are small, nonmotile, intracellular, and aerobic gram-negative bacteria. Of the 10 species that currently form the genus Brucella, 5 were shown to be pathogenic in humans.

**Review Summary:** The epidemiology, clinical manifestations, diagnosis and imaging, and treatment of neurobrucellosis will be reviewed. Brucellosis's transmission to humans occurs by direct contact with contaminated animals. Older patients are at increased risk of nervous system involvement in brucellosis. *Brucella* spp. can lead to central nervous system involvement through direct damage via invasion of neural tissue or indirect damage caused by endotoxins or immune inflammatory reactions elicited by the presence of the bacteria in the body. Patients can have general nonspecific symptoms in addition to neurological and psychiatric symptoms. There are 4 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. For the treatment, a combined therapy is favored over monotherapy for the eradication of Brucella. Moreover, a multirouted therapy has been associated with increased treatment efficacy. The prognosis of neurobrucellosis is dependent on patients' clinical presentation: brucellar meningitis is associated with a good prognosis, whereas diffuse central nervous system involvement is associated with the development of long-term sequelae.

**Conclusions:** Neurobrucellosis affects patients globally and in endemic areas. Neurologists should familiarize themselves with its clinical presentation, diagnosis, and treatment to provide optimal care for their patients.

**Key Words:** brucellosis, neurobrucellosis, review, neurology

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## INTRODUCTION AND EPIDEMIOLOGY

Brucella are aerobic nonspore-forming gram-negative, small, and nonmotile bacteria that reside within cells. Ten species currently form the genus Brucella, with many different serotypes. Of the 10, 5 were shown to be pathogenic in humans. These are *Brucella melitensis*, *Brucella abortus*, *Brucella suis*, *Brucella canis*, and recently, *Brucella marina* by order of pathogenicity.[1,2]

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Brucellosis (Abortus epizootics) is a long-lasting infectious bacterial disease that affects several species of domestic and wild animals, and humans. In Homo sapiens, this illness has many names: Maltese fever, Bang disease, undulant fever, or Mediterranean fever.[2] Globally, Brucellosis, the most frequent zoonotic infection, has an incidence of around 500,000 new cases per year.[3] What is worth noting is its irregular worldwide distribution. As expected, it is more common in countries that lack the minimum standards of uniform successful public health and domestic animal health programs.[3] Regions currently recognized as high risk are the "Mediterranean Basin (Portugal, Spain, southern France, Italy, Greece, Turkey, North Africa), South and Central America, Eastern Europe, Asia, Africa, the Caribbean, and the Middle East."[3] The bacterium was initially discovered in 1887 by David Bruce from the spleen of a soldier's autopsy who died on the island of Malta (hence Maltese fever)[3]; neurobrucellosis was reported for the first time ever by Hughens 9 years later.[4]

Brucella can be spread to humans through different ways. The most common route is by direct contact with diseased cattle or carriers of the disease through wounds, scratches, inhalation of aerosols, or consumption of unpasteurized milk or milk products.[4,5] Other modes of transmission include direct contact with mucous membranes, and airways. Moreover, the bacteria can be transmitted through direct contact with infected placenta, aborted fetus, and amniotic fluid in cattle during gynecologic procedures or during examination and flaying of slaughtered animals.[2] The highest exposure is seen in veterinary doctors and technicians, insemination service employees, zoo technicians, cattlemen who work in private and multiherd farms, and staff of meat processing establishments.[2,3] In a review carried out by Tuon and colleagues, $>60\%$ of the patients who were identified as having acquired the disease from other humans were less than 1 year old. The remaining cases were mainly either transmitted sexually or from blood transfusions.[6]

One of the main obstacles in diagnosing neurobrucellosis is that central nervous system (CNS) infections can have variable presentations. Even though CNS involvement is rare, neurobrucellosis still poses a threat globally and mainly in endemic areas.[2,5] The risk factors related to the expansion of neurobrucellosis are increased age and protracted period of the disease.[5] Most patients presenting with neurobrucellosis are 60 years of age and older. The decreased immunity in older patients increases their risk of nervous system involvement. Multivariate studies showed that sex, nationality, and regional distributions were not aspects associated with the expansion of CNS harm in patients infected with brucellosis.[5] Although brucellosis has no seasonal variation, neurobrucellosis occurs at higher rates in April and May, which is in accordance with the lambing period, and November and December, which is in accordance with the slaughtering time for sheep. Most of the diseased patients are farmers, which points to an inclination of



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the infection to spread to rural, semirural, and unindustrialized areas.[5] Many strategies have been implemented to eradicate this disease from developed and developing countries. The World Health Organization and the World Organization for Animal Health have put forth measures that include, but are not limited to, vaccination and test-and-slaughter programs.[7]

## PATHOGENESIS OF NEUROBRUCELLOSIS

As they penetrate into the human body, Brucella infect the phagocytic macrophages in the reticular connective tissue from which they invade the blood. It is through homogenous spread that bacteria reach the meninges, further proliferating and penetrating into the CNS as the patient's immunity declines. *Brucella* spp. can lead to CNS involvement in 2 main ways: direct damage through invasion of neural tissue, or indirect damage caused by the endotoxins or immune inflammatory reactions elicited by the presence of the bacteria in the body. The latter process was shown to include several immune cells and cytokines that contribute to the damage.[8]

Cytotoxic T lymphocytes were shown to contribute an imperative function in the neuropathology of the disease. In a case of Brucella-associated leukoencephalopathy in a 65-year-old man, cytotoxic T lymphocytes, found in the white matter at high quantities compared with B lymphocytes or the organism itself, mediated the neurological damage due to inappropriate immunologic overactivation and direct cytotoxic injury.[9]

Inappropriate disruption of the blood-brain barrier can also contribute to the development of the disease. This can occur through 2 main mechanisms. First of all, and contrary to the previous beliefs that focused on the reticuloendothelial system as the only target for Brucella organisms, it is now believed that *Brucella* spp. are able to directly invade the brain's endothelial cells. This induces the release of inflammatory cytokines, including interleukin 6 (IL), IL-8, monocyte chemoattractant protein-1, and increased production of adhesion molecules, such as intracellular adhesion molecule-1.

This immune storm establishes an inflammatory profile that can contribute to the neural damage. Furthermore, this state of immunologic overactivation may be achieved through a different mechanism. Brucella organisms can activate the innate immune system of the brain by interacting with astrocytes and microglia. Once activated, these cells release inflammatory cytokines tumor necrosis factor α, IL-1β, and IL-6, which in turn stimulate the brain's endothelial cells. Astrocytes also produce matrix metalloproteinase-9 (by activating intracellular mitogen-activated protein kinase) that further contributes to neural tissue destruction.[10,11]

In addition, animal models suggested that *Brucella* spp. can lead to neurological damage, including Guillain barre syndrome, through a process of molecular mimicry.[12] *B. melitensis* expresses on its surface ganglioside-like molecules that stimulate the production of antiganglioside GM1 antibodies, leading to neurological damage similar to that seen in Guillain-Barré syndrome.[13]

## CLINICAL MANIFESTATIONS

Neurobrucellosis is a multisystem disease. It has a broad spectrum of clinical manifestations. It can occur at any stage of brucellosis and has many clinical neurological symptoms.[4] The onset of symptoms starts manifesting in $<2$ months after infection with Brucella.[14] Patients can have general symptoms, such as fever, myalgia, sweating, low back pain, weight loss, fatigue, loss of appetite, arthralgia, vomiting, and amenorrhea in females. Neurologically, patients mostly present with a severe and persistent headache, one of the most significant hallmarks of neurobrucellosis.[4,14] Patients may also have other clinical manifestations, such as agitation, muscle weakness, disorientation, behavioral disorders, neck stiffness, variations in deep tendon reflexes, apathy, diplopia, blurred vision, and ataxia.[4] Patients can also present with cranial nerves involvement, noncentral facial paralysis, and sensorineural hearing loss.[4,15] Cranial nerves VI, VII, and VIII are the most commonly involved nerves.[16,17] Encephalitis, meningoencephalitis, radiculitis, myelitis, and areflexia are other neurological signs of neurobrucellosis. In addition, patients can suffer from subarachnoid hemorrhage, pseudotumor cerebri, epilepsy, confusion, and incontinence. Interestingly, we found in the literature many case reports of neurobrucellosis manifesting as pseudotumor cerebri, without mention of meningitis being the cause of increased intracranial pressure.[18–20] Neurobrucellosis can also have psychiatric manifestations, such as sleeping complaints and depression.[14,21] It is characterized by white matter lesions along a course of a demyelinating syndrome.[21] Some patients can develop intracranial granuloma, transverse myelitis, spinal arachnoiditis, intracranial vasculitis, and sagittal sinus thrombosis. With respect to the rare manifestation of intracranial granuloma, granulomatous formation results from inflammatory and infectious processes.[16,21] In meningitis, it is crucial to differentiate between brucellar meningitis and tuberculous meningitis.[22,23] In fact, brucella and tuberculosis are both endemic is many countries, including India for example. Both granulomatous diseases can have similar clinical presentation, laboratory parameters, and radiologic findings.[24] As such, it is important to look at specific parameters to differentiate neurobrucellosis and neurotuberculosis. In particular, vestibulocochlear nerve involvement on audiometric tests, lesions in deep gray matter, and extensive white matter demyelinating lesions are all characteristics of neurobrucellosis rather than tuberculosis.[23] However, visual field defects and optic neuropathies are more commonly encountered with neurotuberculosis. In the end, blood cultures and serologic testing are highly specific in determining the offending agent.[25] With respect to brucellar meningitis, the development of basal meningitis induces a lymphocytic pleocytosis ranging between 10 and 200 white blood cells ($mm^3$) in most cases and is below 500 in nearly all cases, which in turn leads to either cranial nerve involvement or intracranial hypertension.[4,14,22,23]

Neurobrucellosis is also characterized by axonal damage, whereby the motor nerve is involved to a greater extent than the sensory nerve and the lower extremities are more affected than the upper extremities.[5] It is noteworthy that one of the most predominantly involved nerve roots is the lumbosacral nerve root because Brucella has a predilection for the lumbosacral area.[4] Tumer and colleagues described in a prospective study the different non-neurological and neurological presentations of brucellosis, which are summarized in Table 1.

Finally, the wide variety of presenting symptoms and clinical manifestations can lead to a delay in both diagnosis and treatment.[4,21]

## DIAGNOSIS AND NEUROIMAGING

There are 4 diagnostic criteria for the diagnosis of neurobrucellosis: signs and symptoms suggestive of neurobrucellosis, a positive finding of *Brucella* spp. from cerebrospinal fluid (CSF) and/or the presence of antibodies directed against brucella in the CSF, lymphocytosis with increased protein levels and decreased glucose levels in CSF, and diagnostic imaging (cranial magnetic resonance imaging or

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**TABLE 1.** Most Common Neurological Findings in Neurobrucellosis Compared to Other Diseases

| | Neurobrucellosis (N = 48), % | Non-neurobrucellosis (N = 80), % |
|---|---|---|
| Headache | 85 | 64 |
| Blurred vision | 23 | 8 |
| Loss of hearing | 19 | 5 |
| Confusion | 10 | 1 |
| Incontinence | 8 | 3 |
| Behavioral changes within the last month | 60 | 13 |
| Agitation | 25 | 10 |
| Muscle weakness | 23 | 4 |
| Disorientation | 21 | 4 |
| Neck rigidity | 17 | 3 |
| Changes in deep tendon reflexes | 10 | 1 |
| Paresthesias | 10 | 1 |
| Apathy | 8 | 3 |
| Dysarthria | 6 | 1 |
| Diplopia | 4 | 0 |
| Ataxia | 4 | 0 |
| Pseudotumor cerebri | 4 | 0 |
| Facial paralysis | 4 | 0 |
| Areflexia | 4 | 0 |

computed tomography) peculiar to neurobrucellosis.[4,16,26] The presence of signs and symptoms consistent with neurobrucellosis in addition to at least any one of the aforementioned criteria is sufficient to diagnose the patient with neurobrucellosis. Lumbar puncture is usually performed when patients experience a severe and persistent headache, hindering their ability to perform daily activities. Patients with insomnia, incontinence, amenorrhea, and clinical findings of neck rigidity, stupor, depression, and alterations in personality are also candidates for lumbar puncture.[4,27] Patients may also undergo audiometric studies, visual field tests, and chest x-rays to rule out possible tuberculosis.[5] An automated system is relied upon to analyze CSF and blood cultures. CSF is subjected to biochemical examination, whereby protein and glucose levels are measured and cells in CSF are counted by a cytometer.[28] CSF protein levels are usually $>45$ mg/dL, the CSF/blood glucose ratio is usually $<0.4$, and leukocytes are mainly lymphocytes.[26,28] In addition, the CSF is subjected to serial dilution using the standard tube agglutination (STA), followed by the Coombs test to detect the Brucella total antibody titers in the CSF. STA and the Coombs test of CSF are highly sensitive and specific serological tests for the detection of brucella antibodies and thus diagnosing neurobrucellosis. Although 2 studies have reported that titers $\geq 1:80$ are enough to report positive antibodies in the CSF, no consensus has been established and many studies still report any titer as a positive result.[28,29] However, patients found to have low titers of STA in CSF with no other criteria are not categorized as having neurobrucellosis.[5] It is noteworthy that enzyme-linked immunosorbent assay (ELISA) used to be a common serologic test for the detection of Brucella in CSF due to its high sensitivity and specificity. Despite being a sensitive and a specific test for the diagnosis of neurobrucellosis, ELISA is no longer commonly used as a diagnostic workup because the STA test has been favored over ELISA over the past few years. However, STA tests should be repeated weekly because immune responses and antibody secretion may be slightly delayed.[14] In addition, the organism can be grown to a lesser extent through culture of the CSF or detected using real-time polymerase chain reaction polymerase chain reaction of CSF samples.[4,30] Moreover, in case of a negative CSF testing, Brucella can be cultured and grown from blood, bone marrow aspirates, and biopsies in the case of hematologic abnormalities and even urine in the case of genitourinary involvement.[28,31,32] With respect to imaging findings, 4 types of imaging results may be encountered: normal findings, inflammation characterized by an abnormal enhancement, white matter changes, and vascular changes. Cranial computed tomography or magnetic resonance imaging may reveal leptomeningeal contrast enhancement, granulomatous lesions, and suspicious nodular lesions.[14]

The main systemic effects of neurobrucellosis can be detected on laboratory workup. Some of the most common findings are elevated alanine aminotransferase and aspartate aminotransferase along with a low red blood cell and platelet count plus variable white blood cell counts.[29,33–35] As for other laboratory findings, the bacterium tends to cause derangements depending on which organ is involved. For example, if there was a genitourinary involvement, pyuria along with a positive urine culture would be expected.[32,36] Similarly, in case there was a neurological involvement, a change in CSF alterations would be expected. The 3 main findings on CSF analysis are mild to moderately elevated protein levels, a mild pleocytosis consisting primarily of mononuclear cells, and a low glucose level.[4,37] Even though CSF adenosine deaminase levels may be elevated in patients infected with tuberculosis, this marker can also be indicative of neurobrucellosis.[38,39] Because there is no clear-cut off value, CSF adenosine deaminase levels are rarely used alone to diagnose neurobrucellosis. However, a spinal tap might be used as the bacterium can be found in CSF culture. On rare occasions, an antibody or agglutination test may be helpful.[4]

## TREATMENT

Treatment options for neurobrucellosis are quite controversial. High relapse rates are observed with monotherapy.[40] Therefore, a combined therapy is favored over monotherapy for eradication of Brucella.[41] Recent reports recommend a combination of rifampicin, doxycycline, and either trimethoprim-sulfamethoxazole or ceftriaxone for an efficient treatment of neurobrucellosis.[40] The duration of treatment varies from 3 to 12 months depending on the CSF response. Rifampicin is administered orally at a dose of 600 mg per day and doxycycline is also administered orally at a dose of 100 mg twice daily. Doxycycline is favored over other antibiotics due to its high CNS penetrance and longer half-life as well.[42] Ceftriaxone is administered intravenously at a dose of 2 g (twice daily). If a patient is allergic to ceftriaxone, levofloxacin hydrochloride (0.4 g intravenously) is administered once on a daily basis for 4 to 6 weeks.[5] Patients using TMP-SMX are usually switched to ciprofloxacin in case of gastric intolerance or if they have any allergic reaction to TMP-SMX. For pseudotumor cerebri, acetazolamide is added to the treatment regimen. Prednisolone is administered in case of cranial nerve involvement and toxicity. Symptomatic relief usually becomes noticeable after 6 weeks of treatment initiation.[28] Thus, treatment efficacy is significantly maximized when using a combined and multirouted therapy.

Limited data are available on the use of corticosteroids in the treatment of neurobrucellosis. Corticosteroids have been shown to be beneficial in the treatment of tuberculous and suppurative bacterial meningitis.[43,44] Most authorities recommend the use of corticosteroids in neurobrucellosis.[15] It has been shown to


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**TABLE 2.** Treatment of Neurobrucellosis in Adults

| Clinical Condition | Treatment |
|---|---|
| Nonpregnant adults (first line) | A combination of*†:<br>Rifampin: orally 600 mg once per day for at least 12 wk<br>Doxycycline: orally 100 mg twice per day for at least 12 wk<br>Ceftriaxone: intravenously 2 g twice per day for at least 4-6 wk‡ |
| Pregnant women | Same as nonpregnant adult but replace doxycycline with trimethoprim/sulfamethoxazole: Orally 160/800 mg twice per day for at least 12 wk |

*In case of pseudotumor cerebri, add acetazolamide.

†In case of peripheral nervous system involvement, add oral vitamin $B_1$ 10 mg 3 times per day for 6 weeks along with intramuscular mecobalamin 500 Ug/d for 6 weeks, and an intramuscular neurotrophic agent 900 IU/d for 2 weeks.

‡In case of ceftriaxone allergy, use intravenously levofloxacin 0.4 g once per day for at least 4 to 6 weeks.

decrease the incidence of long-term complications, in addition to having a protective effect on the tissues from toxins. It should be started a few hours before antimicrobial therapy to avoid possible adverse effects of toxins released from targeted bacteria.[45]

Administration of steroids might be most appropriate in neurobrucellosis complicated by iritis, papilledema, myelopathy, polyneuropathy, and/or cranial nerve palsies.[46]

Finally, the treatment recommendations for pregnant patients will be discussed. One treatment regimen for pregnant patients with neurobrucellosis is ceftriaxone 2 g intravenously twice daily for 4 to 6 weeks, together with a TMP-SMX 1 double-strength tablet orally twice daily and rifampin 600 to 900 mg orally once daily for at least 12 weeks.[47] Because TMP-SMX poses a risk of neonatal kernicterus if used in the last month of pregnancy, pregnant women at $\geq$36 weeks' gestation should be treated with ceftriaxone and rifampin until delivery. Combination therapy is continued after delivery as in nonpregnant adults for a total duration of 12 weeks.[47]

The treatment recommendations are summarized in Table 2.

## PROGNOSIS

The prognosis of neurobrucellosis is greatly dependent upon the clinical presentation. If patients have brucellar meningitis, the prognosis is usually favorable. In case of spinal cord or encephalic involvement, mortality is not uncommon. Patients with diffuse CNS involvement are more prone to developing long-term sequelae.[4,14,41] For instance, sensorineural hearing loss is one of the most common sequelae of neurobrucellosis because Brucella has a predilection for the vestibulocochlear nerve. Motor aphasia, tetra-paresis, and hemiparesis are also common sequelae of neurobrucellosis.[4] Thus, mortality is uncommon, but sequelae are significant. Nevertheless, progression to chronic disease can be offset by adhering to an adequate treatment regimen. An efficient treatment renders the nervous system immune to any possible damage, which significantly reduces the occurrence of ominous sequelae.

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