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### Think about Neurobrucellosis; When a Man Cries!: A Case Study

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#### ABSTRACT

Neurobrucellosis (NB) is a rare and severe form of systemic *Brucella* infection. We introduced an unusual case that “Psychologic Symptoms” was the most prominent complaints of his family. He was a 50-year-old man who has worked in butchery. His problems had begun 2 months prior to his admission with mood disorders, arthralgia, weakness, headache and night sweats; he has recurrent crying with no obvious environmental problem! Wright agglutination test, Coomb’s Wright and 2ME were negative 2 times in outpatient work-ups and the other lab tests weren’t useful in diagnosis. Treatment trials for acute sinusitis and aseptic meningitis have had some improvements of symptoms but his clinical condition was not acceptable. A brain MRI was performed and the results indicated few T2W hyper-signal points of white matter specially periventricular. Brucellosis serologic tests were requested “for third time” and the results were positive. The patient was treated with cotrimoxazole, doxycycline, and rifampicin for 6 months. Two weeks after this treatment, all of mentioned symptoms subsided. Six weeks after treatment the brain MRI was repeated, and the previously seen lesions had improved. The lumbar puncture 3 months after treatment was repeated and results were normal. It is concluded that when a patient in an endemic area suffers from chronic mood disorders, headache, fever, and other non-specific manifestations that cannot be explained by other etiologies, it may be a case of NB. In this case, the “repeated” Wright test and excellent response to NB treatment would confirm the diagnosis.

#### 1. Introduction

Brucellosis is a zoonotic infection that is endemic in Islamic Republic of Iran. This disease is mainly transmitted by contaminated dairy products, such as unpasteurized cheese, milk, and ice cream, by direct contact with infected animals, and by the inhalation of infected aerosolized particles (Tuncel et al., 2009, Najafi et al., 2011). It present as acute, sub-acute and chronic courses by involving different system with varied manifestation

(Shoaee et al., 2008). Neurobrucellosis is a rare and severe form of systemic *Brucella* infection; in 4-13% of patients with Brucellosis, the central nervous system is involved (Lulu et al., 1988, Kochar et al., 2000, Pascual et al., 1988). Brucellosis can present with multiple clinical manifestations in different systems with wide range of complains from asymptomatic disease to the most frequent signs and symptoms such as arthralgia, fever, fatigue, back pain,

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hepatosplenomegaly, focal infection includes osteomyelitis, orchitis, epididymitis, endocarditis, meningitis and myeloradiculopathy (Al-Sous et al., 2004). Many symptoms of Brucellosis occur in different pictures, which may lead to a delayed diagnosis such as neurobrucellosis, that is a presentation of brucellosis and has many clinical manifestations including chronic headache, fever, sweating, and weight loss. The most common feature of neurobrucellosis is aseptic meningitis (Zowghi et al., 2009, Duygu et al., 2012).

Neurobrucellosis (NB) is diagnosed by the presence of any one of the following criteria (Güven et al., 2013):

1. Symptoms and signs of suspected NB
2. Isolation of *Brucella* species from cerebrospinal fluid (CSF) (gold standard) or presence of anti-brucella antibody (Ab) in CSF.
3. Presence of pleocytosis (lymph dominant) high protein and low glucose in CSF.
4. MRI findings such as basal meningeal enhancement, lumbar nerve root enhancement granuloma of the suprasellar region, diffuse white matter change, spinal cord atrophy (Al-Sous et al., 2004).
5. Serum agglutination titer > 1/160 in serum tube agglutination or a positive blood culture.

## 2. Case Presentation

A 50-year-old man who worked in butchery was admitted complaining of headache and fever. His problems had begun 2 months prior to his admission with night sweats, arthralgia, weakness, headache, and mood disorders (depression and change in personality); 5 days before admission he began experiencing headache with fever, nausea, and vomiting. He had outpatient visits in which he was diagnosed with acute sinusitis and treated with 3 doses of ceftriaxone 1 gr/IV and oral co-amoxiclavate 625mg/TDS without improvement.

In the primary physical examination, he was conscious, ill, and febrile. His primary blood pressure (bp) was 120/80mmHg, pulse rate (PR) was 110 beat/min, respiratory rate (RR) was 18/min, and axillary temperature was 38.5°C. In the neurologic examination he had nuchal rigidity with negative Kernig and Brudzinski signs. The patient's lab tests including; liver function test and complete blood cell (CBC) and urine analysis (UA) were normal, erythrocyte

sedimentation rate (ESR) was 20 mm/h, and C - reactive protein (CRP) was 5 mg/dL.

The patient's chest x-ray and brain CT scan were normal. Because of his fever and headache, a lumbar puncture (LP) was performed. The results showed lymphocytic pleocytosis (WBC 40 and lymphocyte 80%), low glucose 43 mg/dL (blood glucose 130 mg/dL), elevated protein levels (90 mg/dL), and negative smear and culture. Based on the LP results and considering his recent treatment with ceftriaxone, the patient was admitted with impression of partially treated meningitis and treated with ceftriaxone and vancomycin. Two days after treatment, the patient was afebrile, but his headache and weakness continued.

Considering his job and history of consuming raw milk, the serum agglutination test for brucellosis was performed, but the results were negative. After two weeks of treatment, the patient has discharged, but his complaints of headache, arthralgia, and depression continued. Two weeks after discharge, the patient returned to the outpatient clinic complaining of headache, severe depression, and changes in behavior. He cried with no obvious environmental problem. A brain MRI was performed; results indicated few T2W hyper-signal points of white matter specially periventricular. A diagnosis of neurobrucellosis included in his differential diagnosis based on the patient's history, job, and recent aseptic meningitis.

The high dilution Wright test was performed, and the result was positive (Wright: 1/80 titer, Coombs Wright: 1/160, 2ME:1/40).

The patient was treated with cotrimoxazole, doxycycline, and rifampicin for 6 months. Two weeks after this treatment, all of mentioned symptoms subsided. The brain MRI 6 weeks after treatment was repeated, and the previously seen lesions had improved. The lumbar puncture 3 months after treatment was repeated and results were normal.

## 3. Discussion

*Brucella* species are gram negative aerobic encapsulated coccobacilli that consist of *B. melitensis*, *B. abortus*, *B. canis*, *B. suis*, *B. ovis*, *B. neotoma* and *B. naris* (Esmaili, 2014, Bennett et al., 2014).

In Iran, *B. melitensis* and *B. abortus* are most common (Bennett et al., 2014). Human

brucellosis is typically acquired through the ingestion of contaminated meat, raw milk, unpasteurized cheese, or ice cream, by inhaling infected aerosol, or through occupational exposure to infected animals (Dean et al., 2012).

*Brucella* have a unique ability to invade both phagocytic and nonphagocytic cells and to survive in the intracellular environment by finding ways to avoid the immune system. This ability helps to explain why brucellosis is a systemic disease and can involve almost every organ system.

*Brucella* can gain entry into the human body through breaks in the skin, mucous membranes, conjunctivae, and respiratory and gastrointestinal (GI) tracts. Sexual transmission has not been convincingly documented. Ingestion usually occurs by way of unpasteurized milk; meat products often have a low bacterial load. In the United States, percutaneous needle stick exposure, conjunctival exposure through eye splash, and inhalation are the most common routes of entry (Rabbani-Anari et al., 2008)

Once within the bloodstream, the organisms quickly become intracellular pathogens contained within circulating polymorphonuclear cells (PMNs) and macrophages, making use of numerous mechanisms to avoid or suppress bactericidal responses. Animal data suggest that the lipopolysaccharide (LPS) coat (smooth in *B. melitensis*, *B. abortus* and *B. suis*; rough in *B. canis*) is likely to play a role in intracellular survival. Brucellosis is caused by infection with *Brucella* species. The traditional classification of these species is based primarily on the preferred host.

Of the 4 *Brucella* species known to cause disease in humans (*B. abortus*, *B. melitensis*, *B. canis*, *B. suis*), *B. melitensis* is thought to be the most virulent and causes the most severe and acute cases of brucellosis and is also the most prevalent worldwide. *B. melitensis* may be acquired via exposure to animals or animal products or, in the case of laboratory technicians, to specimens from animals (including humans) whose tissues are operated

upon or submitted for culture or pathologic analysis ( Table 1) (Bouza et al., 2005).

*B. abortus* is more widely distributed throughout the world than *B. melitensis*, but it is less pathogenic for both animals and humans. It has, however, been the most common cause of brucellosis in North America. This species gives rise to mild-to-moderate sporadic disease that rarely causes complications.

*B. suis* has been the second most common cause of brucellosis in North America. Infection with this species gives rise to a prolonged course of illness, often associated with suppurative destructive lesions.

*B. canis* infection has a disease course that is indistinguishable from that of *B. abortus* infection. It's infection has an insidious onset, causes frequent relapses, and does not commonly cause chronic brucellosis.

Although *B. pinnipediae* and *B. cetaceae* typically affect marine animals, they are now known to be capable of causing disease in humans (mainly neurobrucellosis).

Ingestion of unpasteurized goat milk and related dairy products is the main route by which *B. melitensis* is transmitted to humans.

Slaughterhouse workers, primarily those in the kill areas, become inoculated with brucellae through aerosolization of fluids, contamination of skin abrasions, and splashing of mucous membranes. Farmers and shepherds have similar exposure risks, and they also have exposure to aborted animals. Veterinarians are usually infected by inadvertent inoculation of animal vaccines against *B. abortus* and *B. melitensis*. Laboratory workers (microbiologists) are exposed by processing specimens (aerosols) without special precautions (Lucero et al., 2010).

Occupational exposures tend to be isolated. A large-scale outbreak of the infection should raise suspicion that a biologic weapon has been released, most likely via an infectious aerosol.

Neurobrucellosis occurs more frequently in endemic regions and develops in approximately 5% of cases. Meningitis (1-2%) and, less commonly, papilledema, optic neuropathy, radiculopathy, stroke, and intracranial hemorrhage may be seen (Tena et al., 2006).

Table 1. Currently Recognized Brucella Species

Organism	Animal Reservoir	Geographic Distribution
<i>Brucella melitensis</i>	Goats, sheep, camels	Mediterranean, Asia, Latin America, parts of Africa and some southern European countries
<i>Brucella abortus</i>	Cows, buffalo, camels, yaks	Worldwide
<i>Brucella suis</i>	Pigs (biotype 1-3)	South America, Southeast Asia, United States
<i>Brucella canis</i>	Canines	Cosmopolitan
<i>Brucella ovis</i>	Sheep	No known human cases
<i>Brucella neotomae</i>	Rodents	Not known to cause human disease
<i>Brucella pinnipediae</i> and <i>Brucella cetaceae</i>	Marine animals, minke whales, dolphins, seals	Case reports describing some human cases (mainly neurobrucellosis)

Acute meningoencephalitis presents with a prehospital symptom duration of less than 7 days, and clinical findings progress rapidly. With appropriate aggressive therapy, symptoms resolve quickly, and patients are rarely left with residual sequelae. Other forms of neurobrucellosis typically present after at least 3 months of gradual symptoms. After successful therapy, residual deficits are not uncommon; however, they are rarely debilitating (Keshtkar-Jahromi et al., 2012).

NB is a rare presentation of brucellosis that should be considered in cases where a neurological problem cannot be explained by other etiologies and the patient has a history of living and/or working in or traveling through an endemic area or when similar symptoms can be seen in other family members.

The optimal treatment of NB seems to be 1 month of ceftriaxone 2 gr (IV) twice daily combined with doxycycline a rifampicin for 4-5 months. This regimen provided a low incidence of neurologic complication (Bennett et al., 2014). This regimen should be continued depending on the clinical response and until CSF parameters return to Normal (Erdem et al., 2012). The duration of treatment depends on the patient's condition, but is generally 24 weeks.

This case is a man that was visited many times by a psychologist and a neurologist. He experienced low-grade fever and depression with no suspicions of his history of exposure to cow and sheep and his consumption of raw milk. Therefore, diagnosis and treatment of his case was delayed for 4 months.

#### 4. Conclusion

It may be concluded that when a patient in an endemic area suffers from chronic mood disorder, headache, fever, and other manifestations that cannot be explained by other

etiologies may be a case of NB. In this case, the repeated Wright test and excellent response to NB treatment confirmed the diagnosis.

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