NEUROBRUCELLOSIS PRESENTING WITH HEARING LOSS, GAIT DISTURBANCES AND DIFFUSE WHITE MATTER DISEASE ON BRAIN MAGNETIC RESONANCE IMAGING (MRI)

ABSTRACT • PURPOSE: To report an unusual case of neurobrucellosis.

METHODS: A 48-year-old man was admitted to Rafik Hariri University Hospital (RHUH) for progressive gait disturbances, hearing loss, and some episodes of chills without documented fever. The neurological examination showed gait ataxia, tremor in the legs and mild cognitive decline. The physical exam was otherwise normal.

RESULTS: Magnetic resonance imaging (MRI) of the brain showed diffuse, bilateral, confluent, subcortical, and periventricular white matter disease. Serum agglutination test (SAT) for Brucella was positive in blood and cerebrospinal fluid (CSF). The patient was treated with a combination of ceftriaxone for one month, and doxycycline with rifampicin for one year and his condition stabilized. Literature review was performed. The possible underlying pathophysiological mechanisms are discussed.

CONCLUSION: Neurobrucellosis is a very rare complication of human brucellosis, and can present with a variety of central nervous system symptomatology (CNS) and MRI changes suggestive of leukoencephalopathy. Its diagnosis could be challenging and should always be suspected in patients presenting with CNS manifestations and/or diffuse white matter disease visualized on brain MRI, especially in Brucella endemic areas.

INTRODUCTION

Brucellosis is considered an endemic zoonosis in Lebanon, similar to other countries in the Middle East and elsewhere in the world [1-5]. Data from the Lebanese Ministry of Public Health for the years 2001-2010 indicate a yearly incidence ranging between 156 and 333 cases per year [6]. Several studies from Lebanon reporting on neurobrucellosis appeared in the literature [7-9]. Because of the rarity of this complication, even in an endemic area like ours, this condition remains a challenging diagnostic problem.

Al Sous et al. [10] indicated that the radiological abnor-
Malignancies in neurobrucellosis are usually grouped into three categories: 1) Inflammation, granuloma formation, and enhancement of the meninges and the nerve roots; 2) Vascular insult and inflammatory process of small vessels or venous system leading to small vessel disease, hemorrhages, or venous thrombosis; 3) White matter disease. This latter radiological pattern in neurobrucellosis presents a diagnostic difficulty since it overlaps with other infectious and non-infectious etiologies. Diffuse white matter disease on a brain MRI is often attributed to acute disseminated encephalomyelitis (ADEM) or progressive multifocal leukoencephalopathy (PML) [11]. However, certain infections of the central nervous system (CNS) can have a similar radiological presentation such as cytomegalovirus infection (CMV) [12], pestivirus infection [13], human herpes virus 6 infection [14], acquired immune deficiency syndrome (AIDS) [15] and enteroviral infections [16]. Also, demyelinating diseases and neoplasms should be included in the differential diagnosis [17-18].

Herein, we describe a new case of neurobrucellosis with leukoencephalopathy and discuss the possible pathogenesis of this entity.

CASE REPORT

A 48-year-old man was admitted to Rafik Hariri University Hospital (RHUH) on May 2007 because of progressive gait disturbances and hearing loss. On March 2006, he presented with progressive bilateral hearing loss and vertigo, and was treated symptomatically without any improvement. On November 2006, he developed confusion, spatial disorientation, paresthesias of the right face and arm for around 20 hours with global amnesia of the event. The patient was admitted to another hospital. The working diagnosis was stroke. The following studies were performed: computerized tomography (CT) scan of brain, transthoracic echocardiography (TTE), and carotid duplex ultrasound. All these studies were reported as normal.

Several months later, the patient started to have progressive gait disturbances and aggravation of the hearing loss, and at times chills without documented fever. The general status of the patient was preserved and he did not report any abdominal nor rheumatologic symptoms.

He was then referred to RHUH for further investigations. The patient was diagnosed to have labile hypertension and polycystic kidney disease. He is not used to drinking unpasteurized milk or eating raw meat. On neurological examination, the patient had mild memory problems, bilateral hearing loss, and gait ataxia with postural tremor of the lower extremities. There was no sign of motor or sensory deficits and no meningeal signs. Deep tendon reflexes were normal bilaterally with no Babinski sign. On general examination, the patient was afebrile, with normal heart sounds, chest, and abdominal examination, and with no evidence of lymphadenopathy.

The MRI of brain showed no abnormalities on plain T1 section and after gadolinium injection. However, T2 and FLAIR sections showed bilateral, diffuse, confluent, and hypersignal lesions in the subcortical, periventricular areas, and the temporal lobes as well (Figure 1). Magnetic resonance angiography (MRA) of brain did not show cerebral aneurysms or any other vascular abnormalities. The audiogram showed bilateral sensorineural hearing loss more on the right side and the brainstem evoked responses were absent bilaterally.

Complete blood cell count and results of blood chemical analysis including prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR) were normal. Erythrocyte sedimentation rate (ESR) was 76/first hour. Serum hepatitis B surface antigen (HBsAg), venereal disease research laboratory (VDRL) test, purified protein derivative (PPD), and human immunodeficiency virus (HIV) were negative. Serum levels of antinuclear antibodies (ANA), complements (C3 & C4), anticardiolipin antibodies (ANCA c & p), angiotensin converting enzyme (ACE), anti-Ro/SSA, anti-La/SSB, coagulopathy profile including protein C, protein S, antithrombin III and factor V leiden were normal. Lupus anticoagulant was moderately positive. Cerebrospinal fluid (CSF) was turbid and showed lymphocytosis (White blood cell count: 125/mm$^3$; 64% lymphocytes, 30% segmented, 3% monocytes, 3% eosinophils, 1% basophils, and absence of red blood cells. The CSF biochemical profile showed a high protein level (156 mg/dl), and a low glucose level (37 mg/dl), corresponding serum glucose level, 93 mg/dl).

![Figure 1](image-url)
CSF cultures for bacteria and mycobacteria were negative. Serum agglutination test (SAT) for *Brucella* was positive; titer for *Brucella abortus* was 1/2560 (N < 1/80) in blood, and 1/80 (N < 1/80) in CSF.

The patient received ceftriaxone 1 g IVD BID for one month in addition to doxycycline 100 mg PO BID and rifampin 600 mg PO once daily which were continued for one year. On treatment, his gait improved markedly and he was able to walk without a cane after one month of antibiotic therapy. However, his hearing continued to deteriorate during the first few months and then stabilized. A follow-up MRI of brain performed three months later showed no changes in the radiological pattern.

**DISCUSSION**

Brucellosis is one of the most endemic zoonotic diseases worldwide, especially in the Middle East including Lebanon [3, 7]. Three main *Brucella* species that have predominant animal reservoirs can cause human infections: *Brucella melitensis* (main reservoirs are goats and sheep), *B. abortus* (cattle), and *B. suis* (pigs) [19].

Neurobrucellosis is a very rare complication; it develops in less than 5% of systemic brucellosis cases [20-21]. A landmark publication in 1987 categorized the different clinical presentations of neurobrucellosis [22]. Hence, the central nervous system involvement may be grouped into several categories: meningoencephalitis [23], meningo-vascular involvement resulting in stroke or hemorrhage due to assumed rupture of mycotic aneurysm [24], myelitis [25], polyradiculitis [26], Guillain-Barré Syndrome (GBS) [27], neuritis involving the peripheral or cranial nerves [24], papillitis [28], papiledema and increased intracranial pressure [29], cerebral venous thrombosis [30], and sensorineural hearing loss [31].

The diagnosis of neurobrucellosis is challenging since the presentation could overlap with several infectious and noninfectious diseases. Thus, this complication should be considered in the differential diagnosis of patients presenting with the constellation of the clinical signs and symptoms mentioned above, especially in *Brucella* endemic areas. Blood and CSF cultures, if positive, prove the diagnosis, but their yield is generally low especially in chronic brucellosis; and thus serology is heavily relied upon. Among the serologic tests for brucellosis, ELISA, Indirect Coombs and Brucellacapt (Vir-cell, Granada, Spain) tests are superior to SAT [32-37]. Good clinical outcome on medical treatment further supports the diagnosis.

Treatment generally consists of a combination of two or three of the following medications: rifampin, doxycycline, streptomycin, or trimethoprim-sulfamethoxazole. The duration of therapy for brucellosis is usually 4-6 weeks [38-39]. For neurobrucellosis and other deep seated infections like osteomyelitis, the duration is longer, e.g. up to 15 months [1].

The abnormal radiological findings in neurobrucellosis are not diagnostic; in one report [10], the authors reviewed the brain MRIs of 23 patients with positive *Brucella* titers in their serum and CSF. Diffuse white matter and periventricular changes without the involvement of the corpus callosum were only seen on brain MRIs of seven patients.

We found a case report similar to ours [40]. This report describes the case of a 40-year-old man who presented for recurrent episodes of right-sided weakness, dysarthria, and progressive hearing loss with diffuse bilateral white matter changes without the involvement of the corpus callosum. Extensive workup on this patient was negative except for the titers for *Brucella* using serum agglutination test which were positive in blood and CSF. Another group reported one case of a 65-year-old man, an Iranian immigrant to the USA, who developed a leukoencephalopathy associated with neurobrucellosis [41]. The MRI of his brain revealed bilateral symmetrical T2 signal hyperintensities in the white matter. A brain biopsy of the lesions in the cerebral cortex and white matter showed nongranulomatous meningoencephalitis with reactive microgliosis and astrogliosis. The inflammatory infiltrate was predominantly composed of T lymphocytes, including numerous cytotoxic T cells. There was no evidence of significant myelin destruction. No organisms were detected microscopically, however *B. melitensis* was cultured from the abscess formation drained from the right frontal area and immunoglobulin G titers directed against *B. abortus*, using SAT, were elevated in the cerebrospinal fluid. They concluded that cytotoxic T lymphocytes and microglia activation might play an immunopathogenic role in this rare disease [41].

Herein, we describe another case of serologically documented neurobrucellosis with diffuse, bilateral, subcortical, and periventricular white matter disease on the brain MRI. We believe that the underlying, explicable pathophysiological mechanism in this case is an autoimmune process as advocated by Seidel et al. [41]. This theory is supported by the absence of any acute inflammatory event seen on the brain MRI, which did not show any evidence for disruption of the blood brain barrier or gadolinium enhancement. On the other hand, the significance of the moderately positive *Lupus* anticoagulant antibodies in the serum was not fully understood, especially since the patient did not manifest any thromboembolic events. Studying similar cases and performing extensive laboratory studies for autoimmune markers are needed to support this possibility.

In conclusion, in an endemic area, the diagnosis of neurobrucellosis should always be suspected in patients presenting with a variety of CNS manifestations and/or diffuse white matter disease visualized on brain MRI.

**REFERENCES**

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