

# Neurobrucellosis and venous sinus thrombosis: an uncommon association

**Joana Isabel da Silva Lima<sup>[1]</sup>, Cátia Filipa Gomes Canelas<sup>[2]</sup>,  
Andreia Sofia de Sousa Botelho Trindade Veiga<sup>[3]</sup>  
and Dina Maria Mota Carvalho<sup>[4]</sup>**

[1]. Internato Médico em Oncologia Médica, Serviço de Oncologia Médica, Centro Hospitalar de Trás-os-Montes e Alto Douro, Vila Real, Portugal.

[2]. Internato Médico em Medicina Interna, Serviço de Medicina Interna, Centro Hospitalar de Trás-os-Montes e Alto Douro, Vila Real, Portugal.

[3]. Internato Médico em Neurologia, Serviço de Neurologia, Centro Hospitalar de Trás-os-Montes e Alto Douro, Vila Real, Portugal.

[4]. Serviço de Medicina Interna, Centro Hospitalar de Trás-os-Montes e Alto Douro, Vila Real, Portugal.

### Abstract

Brucellosis is a commonly diagnosed zoonosis and neurological involvement is rare. A 30-year-old woman presented with a pulsatile headache that was exacerbated by the Valsalva maneuver and refractory to analgesic therapy. The patient also had nausea, cough, and coryza that evolved over 7 days. The neurological examination was unremarkable. Thrombosis of the lateral and sigmoid sinus and ipsilateral internal jugular vein were diagnosed and anticoagulation therapy was started. *Brucella spp* was identified in a sample of cerebrospinal fluid (CSF); five months after treatment with rifampicin and doxycycline, CSF was sterile. Cerebral venous thrombosis is a very uncommon sign of brucellosis.

**Keywords:** Brucellosis. Sinus thrombosis. Intracranial.

### INTRODUCTION

Brucellosis is one of the most common zoonoses worldwide, responsible for high morbidity in infected individuals. It has an important economic impact and represents a public health problem in many developing countries<sup>(1)</sup>. Brucellosis is a common infection in regions where the gram-negative bacterium *Brucella spp* is endemic, such as Mediterranean and Middle Eastern countries. Transmission to humans occurs by direct contact with infected animals, inhalation of aerosols, or by ingestion of unpasteurized milk or dairy products<sup>(2)</sup>.

Human brucellosis is a multi-systemic disease, with a broad clinical spectrum, ranging from asymptomatic disease to severe or fatal illness<sup>(1)(2)</sup>. The main presentation is acute febrile illness, with or without signs of localization and chronic infection<sup>(1)</sup>. Neurologic involvement is estimated to be present in 2 to 7% of cases, affecting both the central and peripheral nervous systems with a variety of signs and symptoms<sup>(3)(4)</sup>. The most frequent symptoms are encephalitis, meningoenkephalitis, radiculitis, myelitis, peripheral and cranial neuropathies, subarachnoid hemorrhage, and psychiatric manifestations<sup>(2)</sup>.

Diagnostic criteria for neurobrucellosis are not consensual. According to some authors, the diagnosis can be based on clinical neurological symptoms. Others take into account microbiological and/or biochemical results from cerebrospinal fluid (CSF) samples<sup>(2)</sup>. Reported mortality rates vary between 0-27% and sequelae are often observed despite convenient treatment<sup>(2)</sup>.

Cerebral sinus venous thrombosis is a rare form of stroke (0.5-3% off all cases of stroke), affecting predominantly younger females<sup>(5)</sup>; CNS infections, such as neurobrucellosis, are one possible precipitating factor.

### CASE REPORT

We present the case of a 30 year-old Caucasian female smoker without pathological antecedents and who was using an oral contraceptive. The patient was sent to the emergency room by her general practitioner (GP) because of a pulsatile headache in the right frontotemporal region lasting for three days that was exacerbated by the Valsalva maneuver. She experienced no relief after treatment with several analgesic therapies (paracetamol, tramadol, and Migretil®). No disturbance in the sleep-wake cycle was reported. During the previous seven days, there were also complaints of nausea, cough, and coryza.

On physical examination, the patient was afebrile with no other abnormal findings to report, such as signs of dehydration or systemic hypotension. No cutaneous lesions, such as oral or genital aphthosis, or arthritis were found. The neurological examination was also unremarkable.

**Corresponding author:** Dra. Joana Silva Lima.

**e-mail:** med.joana.lima@gmail.com

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A contrast infusion computed tomography (CT) scan of the head showed a lack of filling in the right lateral sinus and in the ipsilateral jugular vein, indicating the presence of an endoluminal thrombus. There was normal filling of the remaining superficial venous system and deep venous system, and routine blood tests were normal. The patient was hospitalized for etiological investigation and started anticoagulation therapy with low molecular weight heparin.

Serum protein electrophoresis and prothrombotic state, coagulopathy, and autoimmune screening (beta-2 glycoprotein immunoglobulin G (IgG) and immunoglobulin M (IgM), antinuclear antibodies, and rheumatoid factor) results were normal. No monoclonal immunoglobulins were detected. Viral serological test results showed previous immunization against hepatitis B virus, and were non-reactive for hepatitis C virus and human immunodeficiency viruses 1 and 2. Urine microbiology and syphilis test results were also negative.

Brain magnetic resonance imaging (MRI) confirmed right lateral and sigmoid sinus thromboses, as well as a thrombus in the right internal jugular vein (**Figure 1**), without any change in brain parenchyma.

A lumbar puncture was performed and the results excluded possible intracranial hypertension. Cytological and biochemical analyses of a cerebrospinal fluid (CSF) sample were normal. Diagnosis of neurobrucellosis was made upon identification of *Brucella spp* by polymerase chain reaction (PCR).



**FIGURE 1** - Axial cross-section of magnetic resonance image of the patient brain. Filling defect in right lateral and sigmoid sinus and in the ipsilateral internal jugular vein. Sagittal sinus is normal.

All causes of thrombophilia, including permanent and transitory risk factors, were excluded (i.e., severe dehydration; meningitis or meningoencephalitis; autoimmune diseases such as systemic lupus erythematosus, systemic vasculitis, Behçet's disease, anti-cardiolipin, and antiphospholipid antibody syndrome; brain tumors; extracerebral neoplasia; head trauma; dural fistulas; hematological conditions, such as polycythemia and hyperviscosity; nephrotic syndrome; drugs, such as oral contraceptives, methotrexate, and steroids; neurological surgery; previous lumbar puncture; pregnancy; or puerperium). Congenital risk factors, including proteins C and S and antithrombin-III deficiency and factor V Leiden homozygous mutation, were also screened as coagulopathies.

Treatment was performed with rifampicin (900mg per day) and doxycycline (100mg, twice per day). No epidemiologic risk factors were found.

During hospitalization, symptoms improved and the patient was discharged and provided with oral anticoagulants; the patient was subsequently followed at the Neurology and Immunohaemotherapy outpatient clinic.



**FIGURE 2** - Coronal cross-section of magnetic resonance image of the patient brain. Partial recanalization of the right lateral and sigmoid sinus after three months of treatment with rifampicin (900mg per day) and doxycycline (100mg, twice per day).

After 3 months of treatment, a follow-up MRI showed partial recanalization of the right lateral and sigmoid sinuses (**Figure 2**). Almost five months later, lumbar puncture was repeated and *Brucella* was not detected in CSF; antibiotherapy and anticoagulation therapy were suspended.

## DISCUSSION

Presentation with cerebral venous thrombosis and neurobrucellosis is uncommon, with very few cases reported<sup>(6)(7)(8)(9)</sup>. The first description was made in 1999<sup>(10)</sup>. In addition, cerebral vasculopathy due to brucellosis is very rare, and involves the skin, extremities (deep venous thrombosis), aorta, or cerebral vasculature (arterial and/or venous structures)<sup>(6)</sup>.

There are two mechanisms to explain cerebrovascular involvement in neurobrucellosis: a hemorrhagic stroke caused by rupture of a mycotic aneurysm or the inflammatory process of the vessels with consequent lacunar infarcts, small hemorrhages, or venous thrombosis<sup>(6)</sup>.

Laboratory diagnosis can be made using several methods. The most widely used are serological tests, such as the agglutination test<sup>(2)(8)</sup>. However, the rate of *Brucella spp* isolation from CSF is very low, and enzyme-linked immunosorbent assay (ELISA) could be more sensitive<sup>(2)</sup>. In our case, *Brucella spp* detection was performed with PCR, a very sensitive and specific technique.

There is no consensus about choice, dose, and duration of antibiotic treatment for neurobrucellosis. Treatment for at least two months with a combination of two or three drugs that cross the blood-brain barrier, such as doxycycline, rifampicin, trimethoprim-sulfamethoxazole, ciprofloxacin, or ceftriaxone, is recommended. Some studies suggest at least twelve weeks of treatment, depending on the clinical response<sup>(2)(11)(12)</sup>. The sensitivity of *Brucella spp* to third-generation cephalosporins is variable<sup>(2)</sup>. In our case, we followed the most recent recommendations and used a combination of two antibiotics<sup>(2)</sup>. The patient became asymptomatic and CSF tested sterile.

It is important to make an exhaustive investigation of sinus venous thrombosis in young patients even in the presence of transitory risk factors, such as oral contraception since the underlying cause may be due to unexpected infections that can cause permanent damages.

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## Conflict of interest

The authors declare that there is no conflict of interest.

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