



## A unique case of brucellosis with central nervous system vasculitis and literature review

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### Abstract

*Brucella* species are gram-negative, facultative, non-motile intracellular coccobacilli, which replicate inside mononuclear phagocytes. They have zoonotic transmission caused by ingestion of contaminated food, direct contact with an infected animal, or inhalation of aerosols.

**Case Presentation:** A 72-year-old male was admitted to the hospital with a febrile fever of 39.2°C, chills and a 2-week history of urinary urgency. Three days after admission the patient developed new neurological symptoms and signs: confusion, central facial palsy and dysphasia. Brain CT and MRI demonstrated left subacute subdural hematoma, subarachnoid hemorrhage with brain edema and lacunar infarcts.

**Conclusion:** Positive blood cultures and high serologic titer test, followed by fever, severe neurological symptoms, hemorrhagic cerebrospinal fluid, CT and MRI of subdural and subarachnoid hemorrhages as a result of a ruptured aneurism, thrombosis or septic emboli are comparable with neurobrucellosis vasculitis.

**Keywords:** brucellosis, vasculitis, neurobrucellosis, CNS brucella infection

### Introduction

Albeit brucellosis has various clinical manifestations, neurobrucellosis involvement is considered rare, and occurs in 5-10% of cases [1-5]. Furthermore, CNS brucella infection most often presents as either meningitis or meningoencephalitis [6]. In this report, we describe an unusual presentation of neurobrucellosis, where no evidence of meningeal involvement is shown, and which exhibits symptoms of central myelopathy and vasculitis.

### Case presentation

A 72-year-old male was admitted to the hospital with a febrile fever of 39.2°C, chills and a 2-week history of urinary urgency and oliguria. On admission, he was confused and febrile. His systemic and neurological examinations were unremarkable. The patient was suspected for pyelonephritis and urinary retention with the background of benign prostate hyperplasia, and was therefore catheterized and treated with ceftriaxone, amikacin and IV fluids. Three days after admission, his blood culture came positive for brucella. Meanwhile the patient developed new neurological symptoms and signs: deterioration of mental status, confusion, central facial palsy and dysphasia which, a few days later, deteriorated to global aphasia. Brain CT demonstrated subdural collection at the peripheral left hemisphere, which seemed to be a subacute subdural hematoma, with a frontotemporal brain edema. Subsequent cranial MRI verified those findings, in addition to

a mild frontal subarachnoid hemorrhage, with adjacent ischemic changes compatible with lacunar infarcts. Routine blood tests exhibited anemia (hemoglobin 10.6 g/dL), likely due to chronic disease, normal platelet count ( $294 \times 10^3/\text{mL}$ ), high WBC count ( $12.6 \times 10^3/\text{mL}$ ) with neutrophilia (89.3%), elevated C-reactive protein level-101.1 mg/L (normal <0.5 mg/L) and lactate dehydrogenase (462 U/L). Kidney function markers were elevated, blood urea nitrogen (BUN 34 mg/dL) as well as creatinine (2.13 mg/dL). Liver functions and enzymes were normal. In addition to his positive blood culture, his serum agglutinations test for brucella abortus and brucella melitensis were both positive, with a titer of 1/2560 for both. Other serologic tests for vasculitis as ANCA, ANA, Rh factor – were negative. CSF protein was 55 mg/dL, glucose levels were decreased (37 mg/dL). On direct microscopy 33 leukocytes (85% mononuclear), as well as 305 erythrocytes were found in the power field of view. On the basis of his clinical history, microbiological and serological data together with brain CT and MRI findings, cerebral vasculitis due to neurobrucellosis was considered. Because of CNS involvement triple therapy (not double) with Ceftriaxone IV, Doxycycline IV and Rifampicin PO for 6 weeks. Ceftriaxone was used instead of aminoglycosides because of renal failure. During the treatment the patient has clinically improved, however, residual neurological deficits as cognitive disorder, double dysphasia and mild hemiparesis were not resolved.

## Discussion

Brucellosis is one of the most common zoonoses, with over 500,000 cases reported annually, and is considered to be endemic in certain parts of the world, especially in the Middle East and Mediterranean countries<sup>[1-2]</sup>. Once the person gets infected, hematogenous dissemination occurs, and it may reach any organ<sup>[3-4]</sup>.

Worldwide, brucellosis constitutes a major public health hazard in endemic areas. Being a zoonotic infection with high prevalence, reported incidence of human brucellosis varies widely, and reaches 200 per 100,000 in endemic disease areas of population<sup>[7]</sup>. Manifestations of brucella infection are diverse, and are derived from the site where the bacteria had seeded, which can be any organ in the human body<sup>[4]</sup>. Brucellosis infection has been reported in various systems. Osteoarticular, cardiovascular, gastrointestinal, genitourinary, respiratory and nervous involvement were observed<sup>[4-6]</sup>. However, human brucellosis is most commonly presented with high fever, and also characterized by fatigue, malaise, anorexia, headache, stale perspiration, myalgia and arthralgia<sup>[8-9]</sup>.

Vasculitides are characterized by inflammation and necrosis of the blood vessel wall. Diagnosis is based on laboratory and imaging findings. When cerebral affection occurs in systemic vasculitis an acute inflammatory response with raised erythrocyte sedimentation rate and increased values of C-reactive protein is present. In many cerebral vasculitides, including primary angiitis of the central nervous system (PACNS) - CSF studies reveal inflammatory findings.

Most of systemic vasculitides affect small vessels. The small vessel vasculitides may be separated in those with anti-neutrophil cytoplasmic antibodies (ANCA) and those without. Other possible causes of cerebral vasculitis are various infectious diseases such as infectious endocarditis, typhoid brucellosis, systemic auto-immune diseases as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), medications and drugs (amphetamine, cocaine and heroin), some forms of cancer (lymphoma, leukemia and lung cancer) and other forms of systemic vasculitis such as granulomatosis with polyangiitis, polyarteritis nodosa or Behçet's disease. It may imitate a number of complications of other diseases that affect diffusely the blood vessels including the brain - as fibromuscular dysplasia and thrombotic thrombocytopenic purpura<sup>[3]</sup>.

Involvement of the nervous system, though rare, may result with various different pathologies and symptoms. Presentation are divided to both central and peripheral location, and to either acute (< 2 months), subacute (2-12 months) or chronic (< 1 year) course of disease. In addition, it may include any one of several pathologies, such as meningitis, meningoencephalitis, myelopathy, mononeuritis and vasculitis<sup>[10-12]</sup>. Predominantly, CNS involvement of brucella infection, presents as meningitis or meningoencephalitis<sup>[6]</sup>. Interestingly, patients with meningeal manifestations of neurobrucellosis have a higher aptitude to achieve full recovery as opposed to other nervous pathologies<sup>[13]</sup>.

Vasculitis as a potential complication of brucellosis has been well established. The potential affected vasculature is diversified, and include vessels as big as the aorta and as small as small branches of dermis arterioles<sup>[11, 14]</sup>. Both venous and

arterial vasculature may be involved. Most of brucella vasculitic manifestations were reported in the dermis. The first histopathologic evidence for cutaneous vasculitis was shown in 1985 by Franco Vicario *et al*<sup>[15]</sup>. By analyzing the erosive skin tissue of a patient who suffered from acute brucellosis, they demonstrated granulomatous vasculitis in the dermis, with features such as fibrinoid necrosis and thrombosis<sup>[15]</sup>. The mechanism of the thrombosis and its role in the pathophysiology of brucella vasculitis remains unclear. Initially, it was suggested that the vasculitis was a result of a thrombotic process, supported by the presence of thrombi and the lack of evidence of any immunoglobulin or complement deposits<sup>[15]</sup>. However, most of the later reports support the involvement of an immunological process. Various manifestations may result in immune complexes production as a result of brucellosis<sup>[16]</sup>. Glomerulonephritis, hepatitis, arthritis, and vasculitis were all reported to be caused by immunocomplex deposits<sup>[17]</sup>. Specifically, brucella vasculitis was shown as a result of several immunological mechanisms, including IgA deposits, cryoglobulinemia and leukocytoclastic vasculitis<sup>[18-19]</sup>.

Brucella vasculitis was shown to be a particular cause of ischemic stroke and transient ischemic attacks<sup>[20]</sup>. Most probably, the vasculitic pathology has a role in certain ischemic events resulting in neurobrucellosis<sup>[20-21]</sup>. Numerous neurological symptoms were reported in brucella infected patients with evidence of vasculitis. Aphasia, hemiparesis, diplopia, imbalance, cranial nerve palsy were all reported<sup>[22]</sup>. CT or MR imaging shows subdural or subarachnoid hemorrhages or brain infarct. Angiographic imaging often failed to show multiple "cutoff signs" or stenosis of the arteries- findings on digital subtraction angiography. One of those patients had a history of rheumatic heart disease, which further supports an immunological process in the pathophysiology for brucella vasculitis<sup>[22]</sup>.

Certain of the described symptoms were manifested by our patient during his hospitalization. Currently, two possible explanations for the pathophysiology of cerebrovascular involvement in neurobrucellosis can be found. First, a vascular inflammatory process, which results in any of venous thrombosis, lacunar infarct or hemorrhage, as shown by others, as well as in this case report<sup>[20, 23]</sup>. Secondly, brucellar endocarditis, a rare, but well documented, complication of brucellosis<sup>[24]</sup>, could result in a rupture of a mycotic aneurysm, in a mechanism of an emboli of cardiac origin. As shown by Hansmann and Schenken at 1932, post-mortem autopsy demonstrated liquid and blood clots in the subarachnoid space, which originated from a rupture of a mycotic aneurysm in the dorsal wall of the proximal basilar artery<sup>[25]</sup>.

We consider that the enrolled patient had a brucella CNS infection, confirmed by both blood culture and titer test, followed by fever, severe neurological symptoms, comparable with neurobrucellosis as neurological signs and symptoms, CT and MRI of subdural and subarachnoid hemorrhages, frontotemporal brain edema, as a result of ruptured aneurism, thrombosis or septic emboli<sup>[22-23]</sup>. Brain biopsy which is gold standard for diagnosis of vasculitis is a dangerous procedure and has no additional impact on the treatment. The described lesions are not compatible with meningitis or

meningoencephalitis.

Vasculitis is well known in Brucellosis, however neurovasculitis is extremely rare<sup>9-13</sup>, and that makes the described case report unique. We are well aware of the fact that only five reports of cerebrovasculitic neurobrucellosis were presented in the English literature.

### Conclusion

Neurovasculitis is an extremely rare presentation of brucellosis.

Positive blood cultures and high serologic titer test, followed by fever, severe neurological symptoms, hemorrhagic cerebrospinal fluid, CT and MRI of subdural and subarachnoid hemorrhages as a result of ruptured aneurism, thrombosis or septic emboli are comparable with neurobrucellosis even without multiple "cutoff signs" findings of digital subtraction angiography.

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### Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

### Competing interests

The authors declare that they have no competing interests.

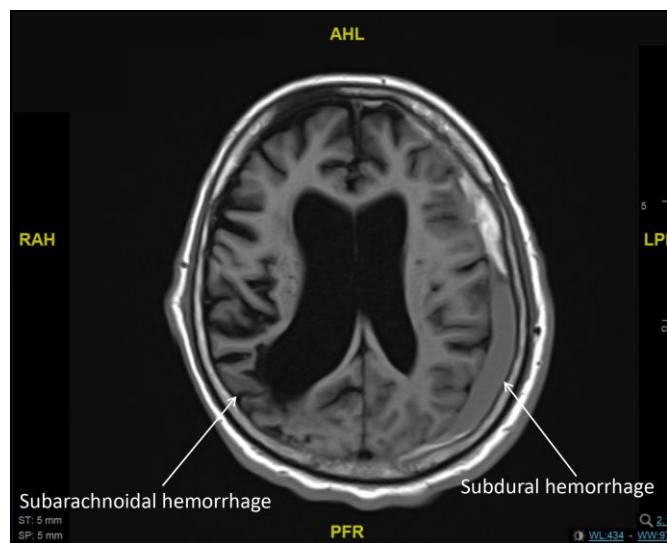


Fig 1

### Authors' contributions

All authors contributed to the treatment of the patient and in writing and final approval of the manuscript. All the authors work in a municipal university-affiliated hospital.

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