*Case report*

# *Brucella* meningitis: first reported case in Egypt

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## Introduction

Brucellosis, an infectious disease transmitted to humans principally through exposure to contaminated milk products, is endemic to the Middle East [*1*]. In Egypt, a cross-sectional study found that 11% of the population had serological evidence of infection with *Brucella* spp., while a study of acute febrile illnesses found that 3% of all bacteraemias were caused by the organism [*2,3*]. *Brucella* spp. has been reported as a cause of meningitis in many parts of the world. But, despite the frequent finding of *Brucella* bacteraemia, as far as we know the agent has not been previously reported in the medical literature as a cause of meningitis in Egypt. The current case thus represents the first report of cerebrospinal fluid (CSF) culture-positive *Brucella* meningitis in Egypt.

## Case report

A 21-year-old Egyptian male was in his usual good health until approximately 2 weeks before admission when he began to complain of anorexia, weight loss, fever, vomiting and headache. Three days prior to admission he developed neck stiffness and diplopia and when the symptoms persisted, he presented to the Abbassia Fever Hospital in Cairo for evaluation.

On examination, the patient was an alert, thin male with a moderately ill appearance. His pulse was 75 beats/min, oral temperature 38 °C, blood pressure 80/120 mmHg and weight 58 kg. Other significant findings were left esotropia, bilateral papilloedema and nuchal rigidity. The remainder of the physical examination, including the neurological examination, was normal.

Peripheral white blood cell (WBC) count was 8000 cells/mL with a differential count of 80% polymorphs. Haemoglobin level was 12.2 mg/dL. After admission, computerized tomography scan of the brain (with and without contrast) was normal, and a lumbar puncture was performed. The CSF sample showed 1650 WBC/mL, 95% lymphocytes, protein 373 mg/dL and glucose 9 mg/dL (Table 1). Samples of blood and CSF were sent to the laboratory for culture. Chest radiograph showed nonspecific exaggerated bronchovascular markings. The patient was not tested for human immunodeficiency virus.

Therapy included parenteral chloramphenicol and penicillin, the Abbassia Fever Hospital standard initial antibiotic regimen for presumed bacterial meningitis [*2*]. When after 2 days the patient showed no response to therapy, isoniazid, rifampicin, streptomycin and pyrazinamide were added to the regimen to empirically treat tuberculous meningitis. On hospital day 11,

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Table 1 **Serial cerebrospinal fluid analysis of the patient with *Brucella* meningitis**

| Test | Day 0 (admission) | Day 1 | Day 7 | Day 14 | Day 35[a] |
|---|---|---|---|---|---|
| White blood cells (cells/mL) | 1650 | 2200 | 1490 | 920 | 320 |
| Polymorphonuclear cells (%) | 5 | 0 | 27 | 0 | 0 |
| Lymphocytes (%) | 95 | 100 | 73 | 100 | 100 |
| Red blood cells (cell/hpf) | 80 | 2400 | 330 | 80 | 0 |
| Protein (mg/dL) | 373 | 367 | 278 | 242 | 197 |
| Glucose (mg/dL) | 9 | 13 | 13 | 32 | 37 |

[a]*14 days after start of anti-*Brucella *treatment.*
*hpf = high-power field.*

*Brucella* spp. was isolated from culture of the CSF sample from admission. *Brucella* tube agglutination tests performed on both serum and CSF samples collected at the time of hospital admission were negative even after high dilution to avoid the prozone phenomenon. Subsequent evaluation using an inhouse enzyme-linked immunosorbent assay (ELISA) test was positive for immunoglobulin (Ig)G and IgM antibodies in the serum, along with IgG antibodies in the CSF (Table 2). Polymerase chain reaction testing of CSF was positive for *B. melitensis*. The patient had some improvement in his clinical condition after anti-tuberculosis treatment, but once the diagnosis of *Brucella* meningitis was made, antibiotic therapy was changed to doxycycline (200 mg/day), trimethoprim/sulfmethoxazole(TMX/SMP) (2 double-strength tablets every 12 hours) and rifampicin (900 mg/day).

Within a week of initiating anti-*Brucella* therapy, the patient became afebrile, had no further vomiting and his esotropia improved. Two weeks after start of therapy for brucellosis, his CSF WBC count decreased to 320 cells/mL, protein level dropped to 197 mg/dL and glucose level rose to 37 mg/dL. All serial CSF parameters are shown in Table 1.

After 1 month of treatment, the laboratory informed the treating physician that the patient's gastric aspirate performed on admission grew acid-fast bacilli on Lowenstein–Jensen slant, identified as *Mycobacterium* spp. The patient was referred to the Chest Hospital for treatment of chest tuberculosis and was lost to follow-up. Prior to transfer to the Chest Hospital, the patient was advised to continue anti-*Brucella* treatment for 3 months.

Table 2 **Pre-treatment serum and cerebrospinal fluid (CSF) *Brucella* antibody titres by enzyme-linked immunosorbent assay and post-treatment CSF *Brucella* antibody titres**

| Serial | Sample | Time after admission (days) | IgM titre (IU/L) | IgG titre (IU/L) | Treatment |
|---|---|---|---|---|---|
| 1 | CSF | 0 | 1/160 | > 1/5120 | Penicillin–chloramphenicol |
| 2 | Serum | 3 | 1/2560 | > 1/5120 | Anti-tuberculosis |
| 3 | CSF | 11 | 1/160 | > 1/5120 | Anti-*Brucella* |
| 4 | CSF | 17 | 1/160 | > 1/5120 | Anti-*Brucella* |
| 5 | CSF | 41 | 1/160 | > 1/5120 | Anti-*Brucella* |

## Discussion

This is the first reported case of *Brucella* meningitis in Egypt and illustrates many of the difficulties in diagnosing chronic meningitis. The initial CSF picture was suggestive of a bacterial process (high WBC count, low glucose and high protein). However, the chronicity of the infection (having symptoms for over 2 weeks before presentation to the hospital) and the preponderance of lymphocytes in the CSF were not the typical presentation of bacterial meningitis. Thus, when no improvement was noted after 2 days of treatment with penicillin and chloramphenicol, which is not the recommended treatment regimen of most scientific sources [*4,5*], therapy was broadened to treat tuberculosis, a common cause of chronic meningitis in Egypt [*2*]. The true diagnosis was not made until the CSF culture yielded *Brucella* spp. 11 days later. The ability to culture the organism from the CSF fluid was a result of clinicians informing the laboratory of the chronic nature of the patient's meningitis, which resulted in the laboratory incubating the fluid past the normal 3-day period.

An additional confusing feature of the case was the improvement in the clinical condition of the patient after anti-tuberculosis therapy was initiated and the negative serum on admission and CSF agglutination test for *B. melitensis* which is a rare phenomenon [*6,7*], leading the practitioners to believe they were treating tuberculous meningitis. This may be because the organism was susceptible to rifampicin and streptomycin, resulting in an initial clinical improvement. Significant further improvement occurred when definitive treatment with doxycycline and TMX/SMP was begun.

Brucellosis is endemic to Mediterranean and Middle East regions [*1,3*]. In Egypt, *B. melitensis* is the most common species and is thought to be transmitted to humans through animal contact and consumption of raw dairy products [*8*]. The exact incidence of *Brucella* spp. infection in Egypt is unknown but in a study of patients admitted to fever hospitals, *Brucella* spp. was second only to typhoid as the cause of acute febrile illness requiring hospitalization [*8*]. A recent cross-sectional study in the Fayoum district of Egypt found the estimated incidence of *Brucella* infections to be 18 per 100 000 persons per year compared to 13 per 100 000 persons per year for typhoid [*9*].

Although *Brucella* infection is common in Egypt and meningitis is a known complication of this infection, we were unable to find any reports of *Brucella* meningitis occurring in the country. In fact, no form of neurobrucellosis, including meningitis, myelitis or radiculoneuritis, has been previously reported from Egypt. As mentioned above, *B. meningitis* has clinical and radiographic characteristics very similar to tuberculous meningitis, and it is difficult to diagnose in the laboratory [*10*]. Although brucellosis is common in Egypt and ELISA is reported to be a sensitive and specific tool to screen for brucellosis [*11,12*], the principal means of diagnosis in Abbassia Fever Hospital is tube agglutination (negative in our case). *Brucella* spp. can take up to 2 weeks to grow, and CSF cultures are routinely inoculated for 2–3 days. Thus the lack of reporting of cases of *Brucella* meningitis in Egypt may be because it is overshadowed by the clinical similarity with the much more common tuberculous meningitis in settings with limited diagnostic capacity.

Incumbent upon physicians diagnosing brucellosis is inclusion of the infection in the differential diagnosis. Brucellosis, among other infections, should be suspected in a patient with symptoms over 10 days, especially if associated with hepatosplenomegaly. Obtaining a history of contact with sheep, goats or cows, and/or consumption of

raw dairy products, significantly increases the likelihood that *Brucella* spp. is the etiology of the infection. Working closely with the laboratory and informing them when unusual etiologies are being considered is mandatory, as demonstrated in this case, since *Brucella* spp. can take up to 2 weeks to grow in culture [*2*] and CSF cultures are routinely only incubated for 2 or 3 days.

In areas at low risk for brucellosis, the presence of an anti-*Brucella* titre strongly suggests the organism is the cause of the infection. However, in endemic areas, while a negative titre can eliminate brucellosis from the diagnosis, a positive titre may represent a past infection and thus is not sufficient to diagnose the infection. However, a titre > 1/160 IU/L, or a rising titre against *Brucella* spp., is highly suggestive of the infection [*12*]. The finding of *Brucella*-specific antibodies in the CSF is also highly indicative of CSF infection. However, since these antibodies are sometimes present at low levels, agglutination tests often employed in the diagnosis of neurobrucellosis can be falsely negative [*13*]. In contrast, the *Brucella* ELISA test is very sensitive, but specificity may suffer due to cross-reaction with other Gram-negative bacteria [*10*]. To decrease the likelihood of false-negative results, some experts advise performing at least 2 different tests to diagnose brucellosis [*1*]. The tests commonly used in clinical practice include the serum agglutination test for screening and then a complement fixation or Coombs test to confirm the diagnosis [*10,14*].

There is little agreement regarding the optimal therapy for *Brucella* meningitis, except for the need for multiple drugs given for prolonged periods. A combination of doxycycline 200 mg/day, rifampicin 900 mg/day and TMX/SMP 2 double-strength tables/day for 4–6 months is recommended [*15*]. Streptomycin 0.75 to 1 g intramuscular per day for the initial 14 days of treatment can be used instead of TMP/SMX. Untreated, the infection is fatal but appropriate antimicrobial regimens result in a high likelihood of cure [*16*]. Although *Brucella* meningitis has a better prognosis and lower mortality than other forms of meningitis, the incidence of minor sequelae is high [*17*].

This case highlights the importance of a broad differential diagnosis of meningitis and the consideration of other etiologies when a patient is not responding as expected. In particular, we suspect the diagnosis of *Brucella* meningitis is much more common than reported based on the prevalence of brucellosis in the community. Clinical suspicion and close collaboration with the laboratory is critical to optimize the ability to diagnose unusual manifestations of infections.

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## Disclaimer

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The study protocol was approved by the Naval Medical Research Unit No. 3 Institutional Review Board in compliance with all applicable Federal regulations governing the protection of human subjects.

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