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CASE REPORT

A Case Report of Meningitis Caused by *Brucella melitensis* Biovar 3

Shuzhu Cao[1,*], Songsong Xie[2,*], Shengnan Song[1,*], Xiu Gu[2], Zhihua Sun[1], Xingmei Deng[1], Jia Guo[1], Tianyi Zhao[1], Yingjin Chai[1], Dexin Zhu[1], Xiafei Liu[3], Xiangwei Wu[2], Hui Zhang[1]

[1]State International Joint Research Center for Animal Health Breeding, College of Animal Science and Technology, Shihezi University, Shihezi, People's Republic of China; [2]NHC Key Laboratory of Prevention and Treatment of Central Asia High Incidence Diseases, The First Affiliated Hospital of Shihezi University, Xinjiang, People's Republic of China; [3]National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Prevention and Control, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xiangwei Wu; Hui Zhang, Email wxwshz@126.com; prof.zhang@foxmail.com

Background: Brucellosis, a major endemic disease in northern China, is contracted by zoonosis of *Brucella*. We report a case of meningitis caused by *Brucella melitensis* biovar 3.

Case Presentation: A 46-year-old man was hospitalized at a local medical facility due to symptoms of fever, soreness, and weakness on April 16, 2021. The local hospital improved the relevant examinations, and the serum tube agglutination test (SAT) for *Brucella* was positive. The patient underwent a week of anti-infective symptomatic treatment with doxycycline and rifampicin, however, his symptoms continued. Subsequently, he was hospitalized in our facility following convulsions and altered consciousness. We conducted several examinations, and the lumbar puncture revealed abnormal cerebrospinal fluid (CSF) protein levels along with a positive culture. Biochemical and polymerase chain reaction (PCR) tests (based on *IS711* gene) identified the pathogen as *B. melitensis* biovar 3. Following treatment involving with moxifloxacin hydrochloride, doxycycline, rifampin, cefatriaxone, mannitol, and dexamethasone the patient's body temperature stabilized, leading to gradual improvements in his clinical status. After two months of the oral anti-infective regimen, the condition is continuing to alleviate and the laboratory indicators returned to normal. The follow-up maintained two years, the patient with no symptomatic recurrences or sequel.

Conclusion: We showed that in epidemic areas of brucellosis, patients with unexplained neurological symptoms should first be examined for neurobrucellosis. Early treatment with corticosteroids and a combination of antibiotics is beneficial for the relief and satisfactory prognosis of neurological symptoms.

Keywords: *Brucella melitensis* biovar 3, meningitis, shepherd, treatment

Background

Human brucellosis, caused by intracellular gram-negative coccobacilli known as *Brucella* species, is recognized as one of the most prevalent zoonotic diseases globally. Among all the species, *Brucella melitensis* is the main pathogenic strain associated with human brucellosis in China.[1] According to the latest data released by the China Centers for Disease Control and Prevention (http://www.chinacdc.cn), a total of 69,767 brucellosis cases were reported in China in 2022, incidence rate of 4.69/100,000, an increase in incidence rate (23.29%) compared to the average of the previous three years (2019–2021) (53,683 cases/year). The Xinjiang Uyghur Autonomous Region (XUAR), which borders eight countries, is an epidemic area with a highly prevalence of brucellosis.[2] In 2022 Xinjiang reported 6,370 cases, ranking second in China, and in 2023 showed a continued rapid rise, with 8,393 cases reported, up 31.76% compared to 2022. *Brucella* infection can affect multiple organs and manifest with a wide range of symptoms, varying from asymptomatic to systemic involvement, including hepatic, cardiac, ocular, and central nervous systems (CNS).[3] Although CNS cases occur in only 4% to 7%, neurologic involvement is the most serious complication.[4] The most common presentation is meningoencephalitis.[5] Moreover, in Xinjiang, China, which is a region with a high prevalence of

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brucellosis and tuberculosis, the diagnosis of neurobrucellosis is an important challenge to differentiate it from neurotuberculosis proper for treatment and outcome.[6,7] However, few studies on meningitis attributable to *Brucella* infection have been conducted in China. In this report, we describe a male patient with meningitis caused by *B. melitensis* biovar 3 who was treated with a combination of corticosteroids and antibiotics.

Case Presentation

A 46-year-old male patient with an unknown-origin fever reaching 38.4°C (self-measurement), weakness, and generalized body soreness was initially presented to the local hospital (People's Hospital of Bortala Mongolia Autonomous Region) on April 16, 2021. The patient, responsible for year-round sheep husbandry, had a medical history of atrial fibrillation for the past 3 years, for which he had undergone an ablation procedure. Upon examination, the serum tube agglutination test (SAT) for *Brucella* was positive, with a titer of 1:400. The patient received doxycycline (100 mg. po.b.i. 24h) and rifampicin (600 mg. ivgtt. q.24h) for anti-infective treatment, but intermittent fever continued.

Six days later, on April 22, 2021, the patient suddenly developed disordered consciousness, speech impairment, and urinary incontinence. Due to the critical condition of the patient, the local hospital recommended his transfer for advanced medical care. He suddenly developed violent limb convulsions lasting for 3 minutes gradually easing. Another convulsion occurred after an interval of 5 minutes during his route to Shihezi at 9 AM on April 23, 2021. Upon arrival, he was admitted to the emergency department of the First Affiliated Hospital of Shihezi University.

We immediately administered anticonvulsant therapy with diazepam injection (20 mg ivp). On admission, a physical examination and laboratory tests were performed. During physical examination, the patient showed a stiff neck and presented with nausea and vomiting. Laboratory tests indicated increases in total protein (8440 mg/dl), total bilirubin (1.60mg/dl), uric acid (10.20 mg/dl), glucose (149.57 mg/dl), creatine kinase (334.6 U/L), lactate dehydrogenase (825.5 U/L), magnesium (2.40 mEq/L), alanine aminotransferase (65.6 U/L), and aspartate aminotransferase (53.1 U/L) levels. An increase in white blood cell (WBC) of 11.3×10^9/L (8.09×10^9/L neutrophils and 19.7% lymphocytes), and a decrease in eosinophilic granulocytes (0.10%) were also observed. The erythrocyte sedimentation rate and C-reactive protein levels were elevated at 23 mm/h and 1.967mg/dl, respectively. Cerebrospinal fluid examination revealed that the intracranial pressure was > 325 mm H_2O (normal range, 80–180 mm H_2O), Pandy's test result was positive, protein level in the abnormal cerebrospinal fluid (CSF) was 155 mg/dl, chloride level had decreased to 386.76mg/dl, and glucose level had decreased to 23.43 mg/dl. In addition, the CT of the head was unremarkable. Baseline electrocardiography showed an ectopic heart rhythm and rapid atrial fibrillation. Mild regurgitation of the mitral valve and incongruous movement of the ventricular wall were observed through TTE. The functions of the liver and thyroid were normal, and indicators of autoimmune diseases were negative. We ruled out *Mycobacterium tuberculosis* infection by conducting T-cell testing for tuberculosis, blood culture and identification, and sputum smear microscopy. Additionally, we tested for cytomegalovirus DNA, *Epstein-Barr* virus, and the nucleic acid of *SARS-CoV-2*, all of which returned negative results. *Brucella* colonies were isolated from CSF) and identified using standard procedures.[8] Phylogenetic analysis revealed that the *Brucella* isolated in this study closely coincided with those of *B. melitensis* biovar 3 isolated from sheep in Xinjiang, China (Figure 1). Upon reconfirmation of the patient's history, we observed that he had been in contact with sick sheep and had not wear protective masks and gloves during feeding and delivery. We postulated that the patient acquired *Brucella* through direct contact or respiratory transmission. Therefore, we suspected that the patient's *Brucella* infection was linked to exposure to the sheep. We detected the strain using PCR with the *IS711* gene and confirmed it as *B. melitensis* (GeneBank: ON09465). The classification of *B. melitensis* biovar 3 was determined by serotyping, phage typing, fuchsin and thionidine sensitivity, CO_2 requirement, H_2S production, and metabolic properties (Supplementary Table 1). This process was completed at the Veterinary Station of the Eighth Agricultural Division of the Xinjiang Production and Construction Corps.

The patient was diagnosed with meningitis caused by *B. melitensis* biovar 3. Cefatriaxone (4 g. ivgtt. q.24h), rifampicin (600 mg. ivgtt. q.24h), moxifloxacin hydrochloride (400 mg. ivgtt.q.24h) and doxycycline (100 mg. po.b.i. 24h) were administered as the initial treatment of infection. The dexamethasone (10 mg ivgtt. q.24h) was used in a gradually decreasing doses regimen and combined with mannitol (125 mL.vgtt.q.8h) to reduce the intracranial pressure. The patient simultaneously received liver-preserving treatment with monoammonium glycyrrhizinate and cysteine and

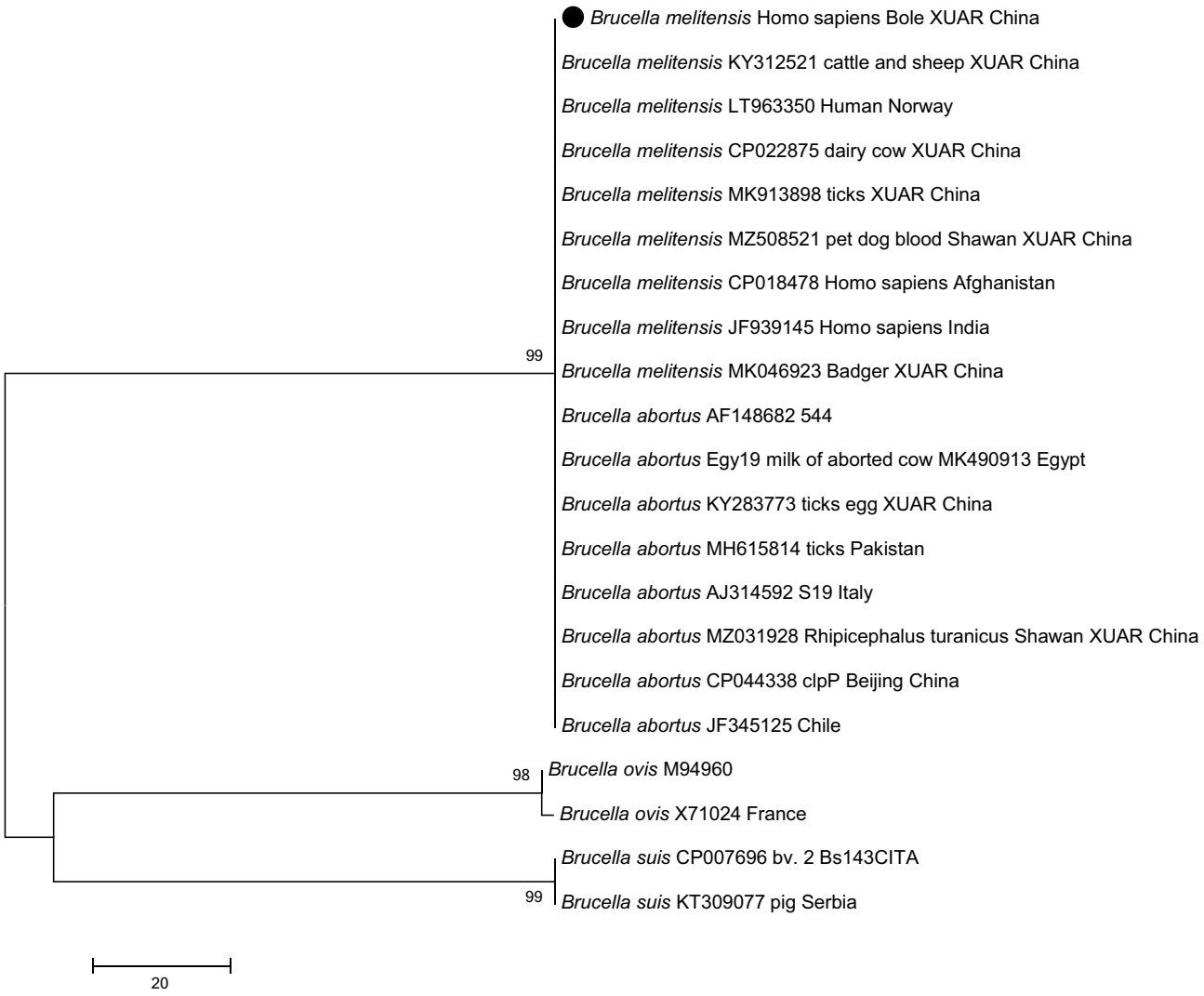

Figure 1 The phylogenetic tree of the *IS711* gene concatenated sequence of *Brucella melitensis* (black dot) isolated from cerebrospinal fluid in this study.

sodium chloride injection (250mL, vgtt.q.24h). After a few days, he demonstrated gradually improvement in consciousness, regained spontaneous respiration, and was able to resume oral feeding by May 6, 2021. His clinical condition gradually improved, and biochemical parameters remained within normal ranges. The patient was discharged with rifampicin (600mg. po. q.24h), moxifloxacin hydrochloride (400 mg. po. q.24h), and doxycycline (100 mg. po.b.i. 24h). The timeline for this case is shown in Figure 2. The oral anti-infective regimen was maintained two months, the pathological symptoms of the patient have basically disappeared, the body temperature was stable, and antibiotics were stopped. The follow-up maintained two years, the patient with no symptomatic recurrences or sequel.

Discussion and Conclusions

Brucellosis, the most common bacterial zoonosis worldwide, is usually transmitted through contact with infected animals or the ingestion of contaminated food.[9] This multi-system disease presents with various clinical manifestations.[10,11] Although the incidence of nervous system involvement is only 2% to 5%, it is the most serious complication involving the central and peripheral nervous systems.[5] In this case, the patient experienced CNS infection with multiple symptoms. The Xinjiang region of China also has a high incidence of tuberculosis,[6] and *Mycobacterium tuberculosis* infections can also involve the nervous system.[7] Therefore, when the patient was transferred to our hospital, we focused on screening for *Mycobacterium tuberculosis* and *Brucella* infections through laboratory and clinical examinations, and quickly

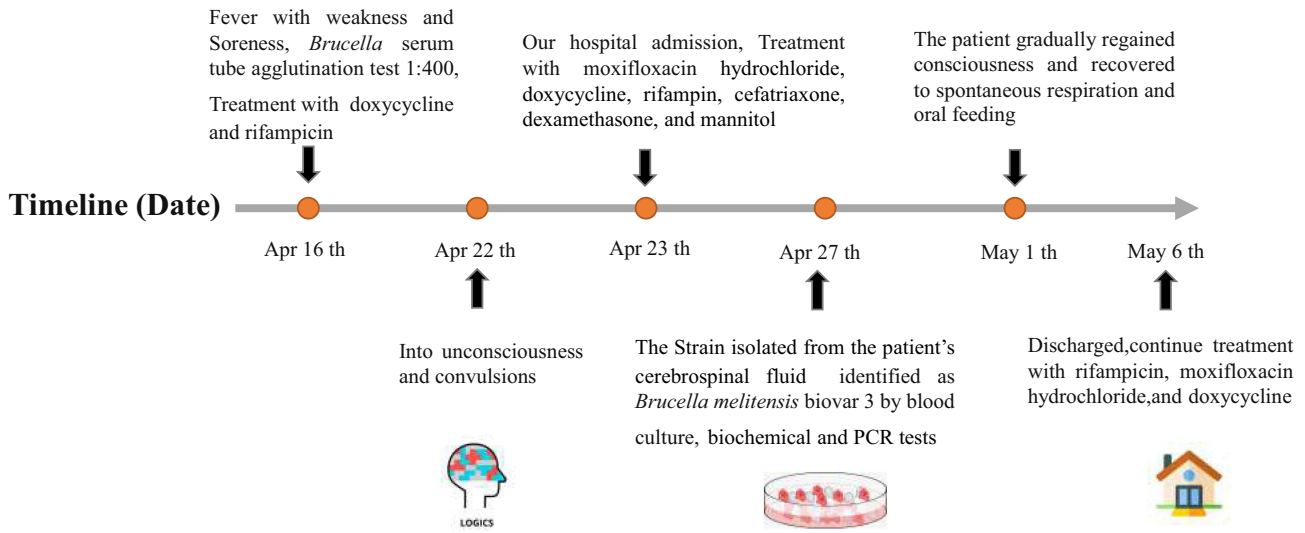

Figure 2 Timeline of the case report.

formulated a symptomatic treatment plan after determining that it was a *Brucella* infection, thus effectively controlling the progression of the disease. This highlights the importance of differential diagnosis.

Neurobrucellosis presents in a variety of ways, such as meningitis, encephalitis, meningoencephalitis, radiculitis, osteomyelitis, optic neuritis, and behavioral abnormalities, with meningitis being the most common, accounting for 17–74% of cases.[3,12] Although CNS involvement is rare, it severely restricts the survival rate of patients without accurate diagnosis and timely treatment. In this case, the patient initially sought treatment at a local hospital for fever, fatigue, and general pain, where they received care for 7 days. Despite receiving anti-infective treatment, the patient's condition did not improve significantly, leading to the progression of the disease meningitis. This underscores the crucial importance of accurate and timely diagnosis in such cases.

Management of neurobrucellosis requires special attention because the illness occurs suddenly with complications, sequelae, and high mortality. Generally, antibiotic regimens include a combination of two or three antibiotics selected from fluoroquinolones, sulfanilamides, tetracyclines, cephalosporins, rifampicin, and amino glycosides.[13] The regimen is often modified several times following developments in symptoms, clinical findings, and the course of the disease. On average, patients with neurobrucellosis are treated for more than three months.[1,13,14] Here, given the early identification of *Brucella* infection, a focused treatment program was promptly devised. The patient received a combination of moxifloxacin hydrochloride, doxycycline, rifampin, cefatriaxone, dexamethasone, and mannitol was administered. Among these, moxifloxacin hydrochloride, doxycycline, rifampin and cefatriaxone have the ability to cross the blood-brain barrier, enabling them to exert an immediately bactericidal effect.[15,16] It is worth noting that the dosage of ceftriaxone (4g. q.24h) sodium used in this case was twice than that of the conventional dosage. We used this quadruple antibiotic combined with corticosteroids and mannitol therapy to effectively control disease development and treated the patient in a relatively short period of time.

Among glucocorticoids, which have good anti-inflammatory effects, dexamethasone has a longer half-life and easily crosses the blood-brain barrier.[17] In our dexamethasone reduction program, we injected 10, 5, and 2.5 mg intravenously on April 23, April 25, and May 1, 2021. The patient's physical condition improved gradually, and all medical indicators returned to normal. A combination therapy with dexamethasone can improve many parameters of bacterial meningitis.[17] Moreover, early treatment with dexamethasone improves prognosis and survival in adults with acute bacterial meningitis and does not increase the risk of gastrointestinal bleeding.[18,19] Among patients with pneumococcal meningitis, 14% of those treated with dexamethasone died and 34% of those treated with placebo died. In addition, patients in the dexamethasone group were significantly less likely to experience impaired consciousness (11% versus 25%), seizures (5% versus 12%), and cardiopulmonary failure (10% versus 20%).[18] These findings explain the significant role of

dexamethasone in the treatment process. Therefore, we suggest the early administration of dexamethasone following confirmation of meningitis.

The identification of the individual strains of *Brucella* is important for epidemiology because of the close association between the individual strains of the genus *Brucella* and their natural hosts.[8] Examples include finding the source of zoonotic infections, epidemiologic investigation of outbreaks, monitoring strains that spread in a specific geographic area and their spread over time, and the distinction between wild-type and vaccine strains. Although there have been some reports of meningitis caused by *Brucella*, few genotypes have been identified.[20–22] To the best of our knowledge, there is only one report of human neurobrucellosis caused by *B. melitensis* biovar 3 in Italy.[14] Moreover, no data are available on the characterization of *Brucella* isolates from humans at the biovar level in China. In previous studies, brucellosis in humans and livestock was mainly caused by *B. melitensis* biovar 3 in XUAR, and in our study, the genotype of *Brucella* is consistent here, which is also *B. melitensis* biovar 3. Current research is limited and we are unable to determine whether *B. melitensis* biovar 3 is more easily crosses the blood-brain barrier than other biovars and cause nervous system infections.Therefore, we recommend that in the management of patients, all isolated strains identified at the species level to determine their biota, which will help us to make targeted control programs tailored to specific for different regions and effectively control the disease.

This is the first reported case of meningitis caused by *B. melitensis* biovar 3 isolated from a shepherd in China. Our study indicates that the genetic features identified in *B. melitensis* biovar 3 will facilitate diagnostic and epidemiological studies on both animal and human brucellosis. However, this case only reports a case of meningitis caused by *B. melitensis biovar 3*, and its species specificity and associated pathogenic mechanism is still unclear, which is our next research direction. Nonspecific findings of neurobrucellosis often make diagnosis difficult. In regions endemic to brucellosis, it is crucial to consider *Brucella* as a potential causative agent in individuals with pre-diagnosed meningitis for timely diagnosis and proper treatment. The antibiotic combined with corticosteroids regimen utilized in this case offers guidance for the treatment of early *Brucella*-induced meningitis. We recommend training in knowledge and skills related to brucellosis prevention in areas with high brucellosis prevalence, as well as routine screening for brucellosis, with a focus on screening high-risk groups such as shepherds, for early detection and treatment.

Data Sharing Statement

All of the data generated or analyzed in this study are included in this published article.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Shihezi University (KJ2020-034-01) approved the study.

Patient Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and the images. Details of the case can be published without institutional approval.

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Author Contributions

Equally contributed to this work as a first author: Shuzhu Cao, Songsong Xie and Shengnan Song. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Cao J, Cai Q, Su W, et al. Case report: metagenomic next-generation sequencing confirmed a case of central nervous system infection with *Brucella melitensis* in non-endemic areas. *Front Med*. 2021;8:723197. doi:10.3389/fmed.2021.723197
2. Zhong Z, Yu S, Wang X, et al. Human brucellosis in the People's Republic of China during 2005–2010. *Int J Infect Dis*. 2013;17(5):e289–e292. doi:10.1016/j.ijid.2012.12.030
3. Karsen H, Tekin Koruk S, Duygu F, Yapici K, Kati M. Review of 17 cases of neurobrucellosis: clinical manifestations, diagnosis, and management. *Arch Iran Med*. 2012;15(8):491–494. doi:10.12158/AIM.0010
4. Shakir R. Brucellosis. *J Neurol Sci*. 2021;420:117280. doi:10.1016/j.jns.2020.117280
5. Rossi M, Tascini C, Carannante N, Di Caprio G, Sofia S, Iacobello C. Neurobrucellosis: diagnostic and clinical management of an atypical case. *New Microbiol*. 2018;41(2):165–167.
6. Li YF, Yang Y, Kong XL, et al. Transmission dynamics and phylogeography of *Mycobacterium tuberculosis* in China based on whole-genome phylogenetic analysis. *Int J Infect Dis*. 2024;140:124–131. doi:10.1016/j.ijid.2023.10.015
7. Patra S, Kalwaje Eshwara V, Pai AR, Varma M, Mukhopadhyay C. Evaluation of clinical, diagnostic features and therapeutic outcome of neurobrucellosis: a case series and review of literature. *Int J Neurosci*. 2022;132(11):1080–1090. doi:10.1080/00207454.2020.1860969
8. Yagupsky P, Morata P, Colmenero JD. Laboratory diagnosis of human brucellosis. *Clin Microbiol Rev*. 2019;33(1):e00073–19. doi:10.1128/CMR.00073-19
9. *Brucella* in raw milk prompts health warning in Texas. *JAMA*. 2017;318(16):1533. doi:10.1001/jama.2017.15338
10. Njeru J, Wareth G, Melzer F, et al. Systematic review of brucellosis in Kenya: disease frequency in humans and animals and risk factors for human infection. *BMC Public Health*. 2016;16(1):853. doi:10.1186/s12889-016-3532-9
11. Abd El-Wahab EW, Hegazy YM, El-Tras WF, et al. A multifaceted risk model of brucellosis at the human–animal interface in Egypt. *Transbound Emerg Dis*. 2019;66(6):2383–2401. doi:10.1111/tbed.13295
12. Gul HC, Erdem H, Gorenek L, et al. Management of neurobrucellosis: an assessment of 11 cases. *Intern Med*. 2008;47(11):995–1001. doi:10.2169/internalmedicine.47.0866
13. Herrick JA, Lederman RJ, Sullivan B, Powers JH, Palmore TN. *Brucella* arteritis: clinical manifestations, treatment, and prognosis. *Lancet Infect Dis*. 2014;14(6):520–526. doi:10.1016/S1473-3099(13)70270-6
14. Sturniolo G, Mondello P, Bruno S, et al. Neurobrucellosis associated with syndrome of inappropriate antidiuretic hormone with resultant diabetes insipidus and hypothyroidism. *J Clin Microbiol*. 2010;48(10):3806–3809. doi:10.1128/JCM.00721-10
15. Akdeniz H, Irmak H, Anlar O, Demiröz AP. Central nervous system brucellosis: presentation, diagnosis and treatment. *J Infect*. 1998;36(3):297–301. doi:10.1016/s0163-4453(98)94279-7
16. McLean DR, Russell N, Khan MY. Neurobrucellosis: clinical and therapeutic features. *Clin Infect Dis*. 1992;15(4):582–590. doi:10.1093/clind/15.4.582
17. Tunkel AR, Scheld WM. Pathogenesis and pathophysiology of bacterial meningitis. *Clin Microbiol Rev*. 1993;6(2):118–136. doi:10.1128/CMR.6.2.118
18. de Gans J, van de Beek D; European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators. Dexamethasone in adults with bacterial meningitis. *N Engl J Med*. 2002;347(20):1549–1556. doi:10.1056/NEJMoa021334
19. Thwaites GE, Nguyen DB, Nguyen HD, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med*. 2004;351(17):1741–1751. doi:10.1056/NEJMoa040573
20. Li X, Wang Q, Gong J, et al. Rare meningitis and epileptic seizure infected with *Brucella* melitensis: a case report. *Clin Lab*. 2019;65(11). doi:10.7754/Clin.Lab.2019.180624
21. Al-Orainey IO, Laajam MA, Al-Aska AK, Rajapakse CN. *Brucella* meningitis. *J Infect*. 1987;14(2):141–145. doi:10.1016/s0163-4453(87)91952-9
22. Liu Y, Gu Y. Case report: a case of abrupt stroke as the first symptom of neurobrucellosis. *Front Neurol*. 2023;14:1066042. doi:10.3389/fneur.2023.1066042