Outbreak Reports

Integrated Approaches of Prevention and Medicine for Dealing with Central Nervous System Brucellosis: A Case from a Non-Epidemic Area — China, 2023

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Summary

What is already known about this topic?

Brucellosis of the central nervous system (CNS) is rare and frequently fatal, often being overlooked or misdiagnosed.

What is added by this report?

In April 2023, the Jinan CDC identified a case of CNS brucellosis in a 54-year-old woman through cerebrospinal fluid (CSF) culture. Upon confirming the diagnosis of brucellosis, the Jinan CDC immediately informed Qilu Hospital of Shandong University, to which the patient had been transferred, and she was subsequently tracked and successfully treated.

What are the implications for public health practice?

The successful outcome can be attributed to the effective integration of a system that facilitated coordinated and collaborative actions between public health services and clinical institutions.

In mid-April 2023, Jinan CDC received a cerebrospinal fluid (CSF) sample from a patient exhibiting symptoms of headache, nausea, vomiting, unconsciousness, and seizures. Initial analysis suggested a potential *Brucella* infection. Following thorough examination, *Brucella* spp. was confirmed, leading to a diagnosis of central nervous system (CNS) brucellosis. Although the patient had been transferred to Qilu Hospital of Shandong University due to deteriorating health, Jinan CDC provided crucial information to the hospital's Infectious Disease Department, ensuring the prompt administration of appropriate anti-*Brucella* treatments. This collaborative approach, facilitated by the "Qilu Medicine-Prevention Innovative Integration" pathway, enabled the patient's rapid recovery without subsequent disabilities. This case underscores the effectiveness of continuous communication and information sharing between healthcare facilities in managing infectious diseases.

INVESTIGATION AND RESULTS

In March 2023, a 54-year-old woman presented at a local clinic with moderate headache, nausea, and vomiting, but no fever. Despite lacking a significant medical history, cerebrovascular disease was suspected based solely on her symptoms. She was treated with intravenous fluids as opposed to antibiotics, yet her condition did not improve. Two weeks later, she displayed irritability and incoherent speech. Subsequent evaluation at a county-level People's Hospital, where a craniocerebral CT scan ruled out acute hemorrhage, revealed no definitive cause of her symptoms. That night, she experienced a seizure characterized by upward eye movements, clenched teeth, limb stiffness, and altered consciousness, lasting approximately one minute and resolving spontaneously. She regained full consciousness after about ten minutes. The following day, she developed convulsions, delirium, and a slight fever, which led to her transfer to another hospital's Emergency Department on April 14, 2023. A craniocerebral magnetic resonance using a diffusion-weighted imaging (DWI) sequence did not show any acute cerebral infarction. Analysis of CSF indicated an elevated white blood cell count of 353×10^6/L, with 82% mononuclear cells and 18% polymorphonuclear cells. *Brucella* spp. was suspected in the CSF sample, which was sent to Jinan CDC for confirmation. Initially treated with diazepam, mannitol, sodium valproate, acyclovir, and ceftriaxone, her condition continued to deteriorate, necessitating further management at the Department of Neurology of Qilu Hospital, Shandong University.

Brucella melitensis was isolated from a CSF sample sent to Jinan CDC, confirming brucellosis. The Infectious Disease Department at Qilu Hospital was promptly notified via the "Qilu Medicine-Prevention Innovative Integration" pathway (Figure 1). The

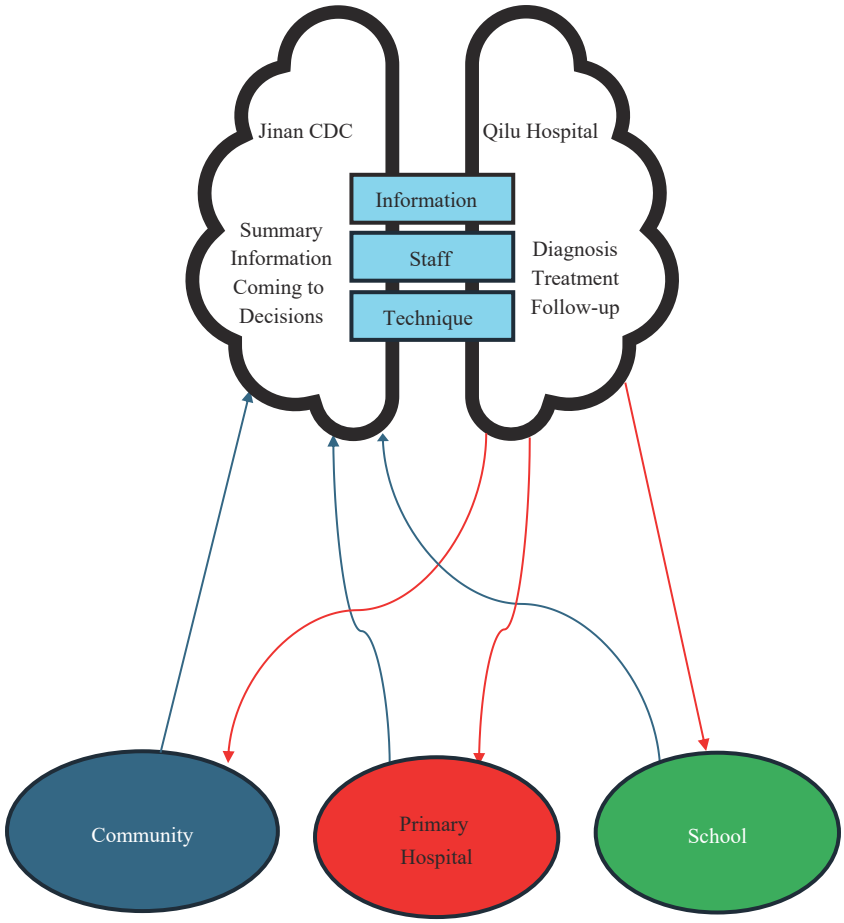

FIGURE 1. "Qilu Medicine-Prevention Innovative Integration" pathway.

patient was then transferred to the same department at Qilu Hospital. Treatment for CNS brucellosis was initiated with doxycycline (0.1 g po. b.i.d.), rifampicin (0.45 g po. b.i.d.), and ceftriaxone (IV every 12 h), supplemented with mannitol to reduce intracranial pressure. The blood test for brucellosis antibodies was positive. The patient's peripheral blood leukocyte count was recorded at 6.15×10^9/L, with neutrophils constituting 76.50% of the leukocytes. The C-reactive protein level was 3.67 mg/L. Tests for serum electrolytes, liver function, thyroid function, and autoimmune disease markers were all within normal limits. Additional diagnostics, including TB IFN-γ release assay, antineutrophil cytoplasmic antibodies, anticardiolipin antibody assay, lymphocyte subset assays, echocardiography, and lumbar magnetic resonance imaging (MRI), revealed no significant abnormalities. Given her history of consuming barbecued foods, she was diagnosed with a CNS infection caused by *Brucella*, which was associated with secondary epilepsy.

Three days following treatment initiation, the patient regained normal consciousness and experienced no further convulsions. A subsequent lumbar puncture performed one month later revealed a reduced white blood cell count in the CSF, and cultures were negative for *Brucella*. The patient then underwent oral anti-infective therapy for approximately seven months, during which her symptoms resolved. CSF karyocyte counts eventually normalized (Table 1), leading to the discontinuation of antibiotics (Figure 2).

PUBLIC HEALTH RESPONSE

Jinan CDC conducted screenings on all high-risk populations using culture and serological tests, with a total of 12 individuals tested and no infections detected. Medical institutions across Jinan were provided training to enhance their diagnostic and treatment capabilities for brucellosis. Additionally, health education on brucellosis was provided to all practitioners and the general public.

TABLE 1. Diagnostic workup of the cerebrospinal fluid sample during the treatment period.

Parameter (unit)	Results for three dates			Normal range
	Apr 28	May 18	Nov 7	
Karyocyte count (10^6/L)	144	64	8	0–8
Small lymphocytes (%)	98	98	98	70
Lactate (mmol/L)	1.60	1.80	1.80	1.20–2.10
CSF protein concentration (g/L)	1.41	1.12	0.62	0.15–0.45
Chloride (mmol/L)	115	117	129	120–130
Glucose (mmol/L)	2.58	2.75	2.81	2.80–4.50

Abbreviation: CSF=cerebrospinal fluid.

DISCUSSION

In this report, we describe a rare case of CNS brucellosis identified in a region not typically endemic for this infection. Brucellosis is a neglected zoonosis caused by the pathogenic bacterium *Brucella* (*1*) and may be transmitted to humans through direct or indirect contact with infected animals or by consuming their contaminated products (*2*–*3*). The infection in this patient likely originated from consuming barbecued meat. The detection of this case emphasizes the potential need for enhanced screening of suspect animal products.

Brucella is recognized for causing systemic diseases in humans, with CNS involvement being an uncommon manifestation. Consequently, the atypical clinical signs observed in patients frequently lead to misdiagnosis or inappropriate treatment (*4*–*5*). The current case was identified as CNS brucellosis due to a progression of symptoms beginning with headache, vomiting, and delirium; this contrasts with typically reported symptoms of CNS brucellosis, which include headache, fever, and confusion (*4*–*5*). Without precise diagnosis and prompt treatment of CNS involvement, the prognosis for brucellosis patients remains poor, highlighting the importance of early detection (*2*–*4*).

Although *Brucella* infection can be diagnosed through culture, serological testing, and polymerase chain reaction (PCR)-based methods, culture is still considered the gold standard for diagnosis (*4*–*5*). However, the sensitivity of cultures is low, and confirmation by the CDC is often required. Serodiagnosis of brucellosis does not offer direct evidence of the microorganism's presence. Despite the high sensitivity of real-time PCR assays, a positive result does not always indicate an active infection. *Brucella*-specific serodiagnostic assays and nucleic acid amplification tests may not be conducted if the disease is not initially considered, potentially leading to missed diagnoses (*5*). In the case described, the initial diagnosis was based on symptoms. Following the patient's presentation with disturbances in consciousness, CSF was examined, allowing for the isolation of *Brucella* in the CSF. Although lymphocytic pleocytosis was prevalent in 90% of CNS brucellosis cases, approximately 10% exhibited a predominance of CSF polymorphonuclear cells. It is important to note that CSF lymphocytosis is not specific to neurobrucellosis, as it is also observed in other types of meningitis, including tuberculosis and neurocryptococcosis.

CNS brucellosis is typically managed with a combination of doxycycline, rifampicin, and ceftriaxone. However, there is no established consensus regarding the choice of antibiotic, dosage, and treatment duration for neurobrucellosis. Some studies have reported continuing antimicrobial treatment for 4–9 months. Regimens based on ceftriaxone have shown greater success with shorter treatment durations compared to the standard oral treatment protocol (*4*).

Patients with diffuse CNS involvement exhibited worse prognoses, often resulting in frequent sequelae (*4*). The favorable outcome observed in this high-risk case of CNS brucellosis can be attributed to the timely diagnosis and treatment facilitated by an integrated system that involved coordinated collaboration between public health services and clinical institutions (Figure 1).

The establishment of an integrated medicine and prevention service system, which provides continuous services, enhances early disease diagnosis, prompt disease management, and reduces healthcare costs. Effective communication and information sharing among primary healthcare facilities, public hospitals, and public health institutions, coupled with the development of early warning systems, augment the system's agility and response capability to health risks (*6*–*7*). Through this collaborative framework, medical

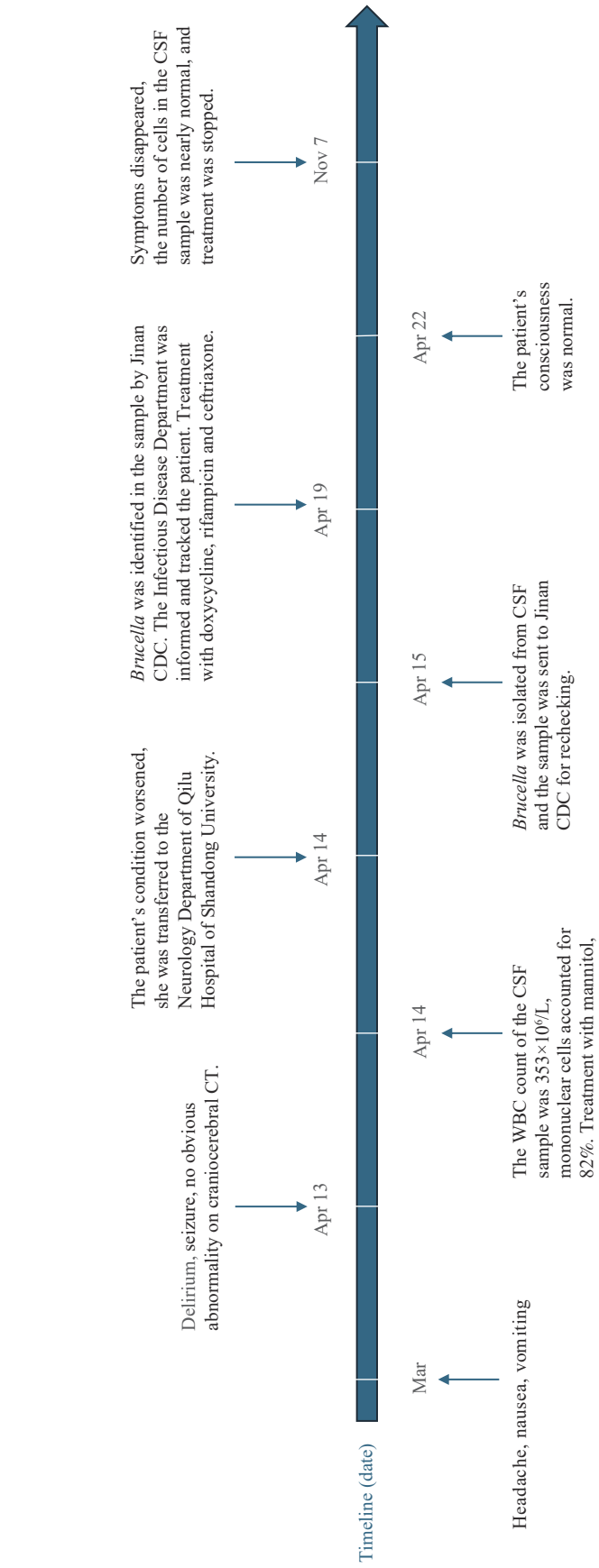

FIGURE 2. Timeline of the case report.
Abbreviation: CSF=cerebrospinal fluid.

institutions leverage shared technological and resource advantages to swiftly and accurately identify high-risk cases and report them to public health authorities. Consequently, these institutions can rapidly initiate epidemiological investigations and laboratory tests, assess risks meticulously, and inform hospital staff to implement appropriate treatment protocols (Figure 1).

In conclusion, the findings from this case emphasize the necessity for coordinated healthcare services across various levels and locations within and beyond the health sector, tailored to patient needs throughout their lifespan (*8*–*10*). Furthermore, integrating treatment and prevention services enhances patient-centered healthcare and integrated medical care, facilitating timely treatment through rapid diagnosis, particularly for rare infectious diseases.

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REFERENCES

1. Welburn SC, Beange I, Ducrotoy MJ, Okello AL. The neglected zoonoses--the case for integrated control and advocacy. Clin Microbiol Infect 2015;21(5):433-43. http://dx.doi.org/10.1016/j.cmi.2015.04.011.
2. Pappas G, Akritidis N, Bosilkovski M, Tsianos E. Brucellosis. N Engl J Med 2005;352(22):2325 – 36. https://doi.org/10.1056/NEJMra050570.
3. Franco MP, Mulder M, Gilman RH, Smits HL. Human brucellosis. Lancet Infect Dis 2007;7(12):775 – 86. https://doi.org/10.1016/S1473-3099(07)70286-4.
4. 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):165-7. https://www.newmicrobiologica.org/PUB/allegati_pdf/2018/2/165.pdf.
5. Yagupsky P, Morata P, Colmenero JD. Laboratory diagnosis of human brucellosis. Clin Microbiol Rev 2019;33(1):e00073 – 19. https://doi.org/10.1128/CMR.00073-19.
6. Yang H. Cooperated and shared care: reflections on treatment-prevention integration. Chin Gen Pract 2023;26(22):2711 – 4. https://doi.org/10.12114/j.issn.1007-9572.2022.W0006.
7. Beaglehole R, Bonita R, Horton R, Adams O, McKee M. Public health in the new era: improving health through collective action. Lancet 2004;363(9426):2084 – 6. https://doi.org/10.1016/S0140-6736(04)16461-1.
8. Koo D, Felix K, Dankwa-Mullan I, Miller T, Waalen J. A call for action on primary care and public health integration. Am J Public Health 2012;102 Suppl 3(Suppl 3):S307-9. http://dx.doi.org/10.2105/AJPH.2012.300824.
9. Kringos D , Boerma W , Hutchinson A ,et al.Building primary care in a changing Europe: case studies[M]. 2015.
10. Schot E, Tummers L, Noordegraaf M. Working on working together. A systematic review on how healthcare professionals contribute to interprofessional collaboration. J Interprof Care 2020;34(3):332 – 42. https://doi.org/10.1080/13561820.2019.1636007.