

Ischemic Stroke as a Rare Manifestation of Neurobrucellosis: A Case Report

Yang Zhou^{1,*}, Minghui Yun^{1,*}, Xiaocui Han^{2,*}, Chunlei Chen², Chao Wei¹, Ping Huang³, Xinhuan Feng⁴, Jing Chen⁵, Songsong Xie^{1,6,7}

¹NHC Key Laboratory of Prevention and Treatment of Central Asia High Incidence Diseases, The First Affiliated Hospital of Shihezi University, Shihezi, Xinjiang, 832000, People's Republic of China; ²Department of Infectious Medicine, the Sixth Division Hospital, Xinjiang Production and Construction Corps, Wujiaqu, 831300, People's Republic of China; ³Department of Infectious Diseases, Yanqi Hospital of the Second Division, Xinjiang Production and Construction Corps, Yanqi, 841100, People's Republic of China; ⁴Department of Infectious Diseases, the People's Hospital of Yining, Yining, Xinjiang, 835000, People's Republic of China; ⁵Department of Infectious Medicine, The Second People's Hospital of Yining, Yining, Xinjiang, 835000, People's Republic of China; ⁶State Key Laboratory for Diagnosis and Treatment of Severe Zoonotic Infectious Diseases, Wuhan, 430000, People's Republic of China; ⁷The Clinical Research Center for Infectious Diseases of Xinjiang Production and Construction Corps, Xinjiang Production and Construction Corps, Shihezi, 832000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Songsong Xie; Jing Chen, Email xss2024@126.com; 18899555017@163.com

Background: This article presents a case report of a patient with neurobrucellosis (NB) complicated by ischemic stroke (IS).

Case Presentation: A male presented with new-onset left-sided limb weakness lasting three days, along with a 15-month history of intermittent fever and progressive right-sided limb weakness over eight months. A cranial MRI revealed an acute infarction in the left cerebellar vermis. Cerebrospinal fluid (CSF) analysis revealed elevated protein levels and pleocytosis. Next-generation sequencing (NGS) of the CSF detected 1469 *Brucella* species. Polymerase chain reaction (PCR) testing for the *Brucella* OMP22 gene was positive in the patient's urine, CSF, and blood samples. Following combination antimicrobial therapy with doxycycline, rifampicin, and trimethoprim-sulfamethoxazole (TMP-SMX), the patient's clinical symptoms progressively improved, and laboratory parameters normalized.

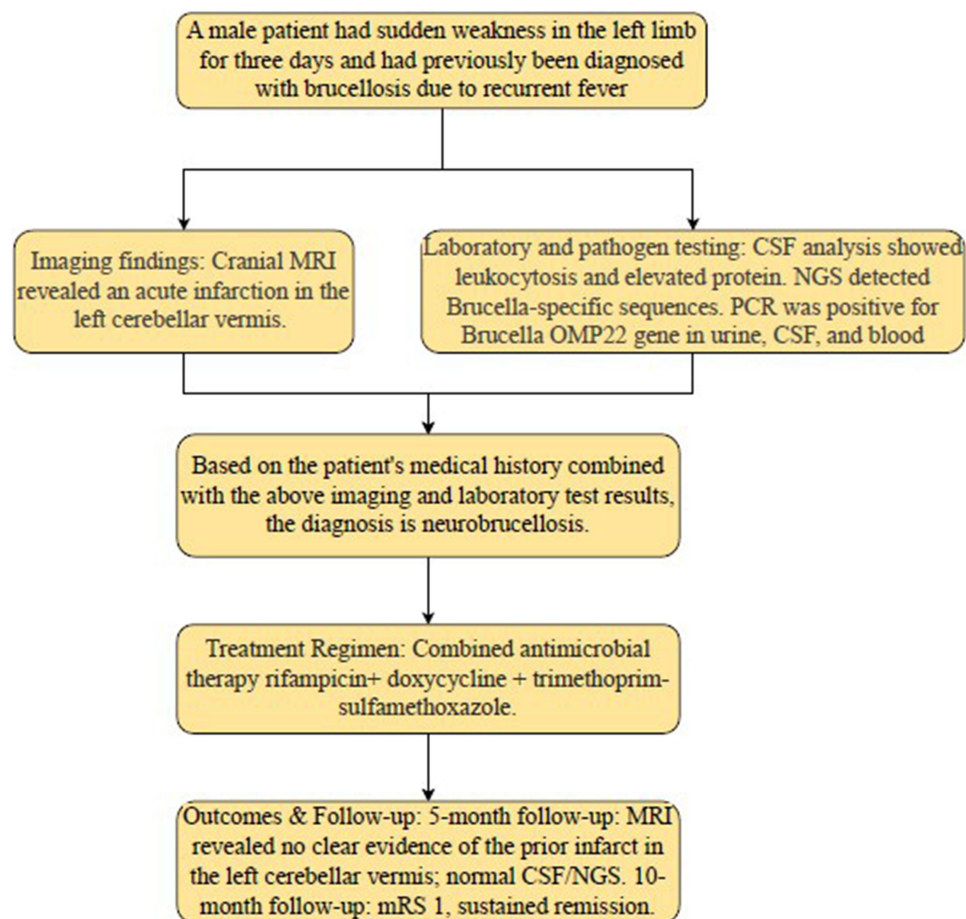
Conclusion: This case underscores the importance of considering NB in the differential diagnosis of patients presenting with unexplained symptoms in brucellosis-endemic regions. Early diagnosis and combined antibiotic therapy are critical to alleviating NB symptoms and improving clinical outcomes.

Keywords: neurobrucellosis, stroke, OMP22, treatment

Background

Brucellosis is one of the most common zoonotic diseases worldwide, with approximately 2.1 million new cases reported annually.¹ Neurobrucellosis (NB), a neurological complication of brucellosis, occurs in about 4% of cases and presents with heterogeneous clinical features. Due to the absence of pathognomonic signs, NB is often misdiagnosed as other infectious or neurological disorders.² Brucellosis infection of the central nervous system (CNS) is a rare but severe complication, and the varied clinical manifestations, including confusion, meningoencephalitis, myelitis, peripheral or cranial neuropathies, and psychiatric manifestations, make the diagnosis challenging. Furthermore, when *Brucella* invades cerebrovascular tissue, it can manifest as ischemic infarction and transient ischemic attack, which are also relatively rare symptoms.^{3,4} Ischemic stroke (IS), subarachnoid hemorrhage, and mycotic aneurysms are recognized meningovascular complications of NB. Patients may also present with cranial nerve involvement, peripheral facial palsy, and sensorineural hearing loss.⁵ The stroke mechanisms in NB are mainly attributed to small vessel vasculitis. Inflammatory vascular events can result in lacunar infarcts, hemorrhagic strokes, or cerebral venous thromboses.⁶ In China, brucellosis is predominantly endemic in pastoral regions such as Xinjiang, Inner Mongolia, and Qinghai.⁷ In 2024, Xinjiang reported 8138 cases (<https://wjw.xinjiang.gov.cn>), ranking second in the country for disease incidence.

Graphical Abstract



However, studies on brucellosis-associated IS remain scarce in China. This article presents a case of brucellosis complicated by IS, aiming to provide clinicians with valuable insights for identifying the underlying causes of unexplained stroke and enhancing their understanding of NB.

Case Presentation

The patient was first hospitalized in June 2024 for recurrent fever and diagnosed with brucellosis via a serum agglutination test (SAT) with a titer of 1:400. He completed a 6-week course of doxycycline (100 mg orally twice daily) and rifampicin (600 mg orally once daily). However, the fever persisted intermittently without follow-up. In October 2023, he was readmitted to the Department of Neurology for sudden onset of right-sided limb weakness. A cranial MRI showed no evidence of infarction, leading to a diagnosis of “MRI-negative cerebral infarction”, and he was started on dual antiplatelet therapy with aspirin and clopidogrel.

On June 22, 2024, the patient developed left-sided limb weakness. Three days later, on June 25, he was admitted for the third time due to worsening symptoms. Neurological examination revealed left central facial paralysis with intact extraocular movements. Muscle strength was normal in the right upper extremity, with the left upper extremity at 4/5 grade, and both lower extremities at 4/5 grade. No pathological reflexes were observed, including negative Babinski’s, Chaddock’s, and Kernig’s signs, and Hoffmann’s sign was negative. The patient’s National Institutes of Health Stroke Scale (NIHSS) score was 4, the water swallow test (WST) result was grade 2, and the modified Rankin Scale (mRS) score was 2. A cranial MRI, performed on June 25, 2024, revealed an acute infarct in the left cerebellar vermis, with

striated hyperintensity on DWI (measuring approximately $2.5 \text{ cm} \times 1.0 \text{ cm}$), hypointensity on T1WI, hyperintensity on T2WI, and slightly hyperintensity on FLAIR, which was consistent with the manifestation of cytotoxic edema. The lesion was located in the blood supply area of the left posterior circulation. (Figure 1).

Laboratory tests on June 25, 2024, showed elevated absolute monocyte count ($0.74 \times 10^9/\text{L}$; reference range: $0.1\text{--}0.6 \times 10^9/\text{L}$), decreased serum urea (2.9 mmol/L ; reference range: $3.6\text{--}9.5 \text{ mmol/L}$), and decreased creatinine ($48 \mu\text{mol/L}$; reference range: $57\text{--}111 \mu\text{mol/L}$). All other tests, including liver function, T-cell spot test, fecal occult blood, CRP, urinalysis, stool analysis, and blood cultures with sensitivity, were within normal limits. Bacterial smears (using whole blood), acid-fast bacilli smears (using sputum), and Epstein-Barr virus (EBV) DNA quantification and cytomegalovirus (CMV) DNA testing (both using whole blood) were all negative. These results help to exclude common bacterial infections, active tuberculosis, and acute EBV or CMV infections.

Following consultation with the neurointerventional surgery team, the patient was diagnosed with cerebral infarction but deemed ineligible for thrombolytic therapy. A lumbar puncture was performed on June 29, 2024, and cerebrospinal fluid (CSF) was submitted for next-generation sequencing (NGS). CSF analysis showed marked leukocytosis ($69 \times 10^6/\text{L}$), significantly elevated protein levels (2042.6 mg/dL), decreased glucose (2.38 mmol/L ; reference range: $2.40\text{--}4.50 \text{ mmol/L}$), and reduced chloride (115 mmol/L ; reference range: $120\text{--}130 \text{ mmol/L}$).

The patient was treated with antiplatelet therapy, lipid-lowering agents, and circulation-enhancing medications. Repeat cranial imaging on July 2, 2024, showed that the infarction in the left cerebellar vermis, presenting as a patchy abnormal signal, measured approximately $1.0 \text{ cm} \times 0.8 \text{ cm}$, which indicated improvement compared to the previous scan (Figure 1). However, the patient's limb weakness persisted. On July 3, he developed a fever (peak temperature 38.4°C) accompanied by confusion. NGS results, received the same day, identified 1469 *Brucella*-specific sequences. Polymerase chain reaction (PCR) results for the *Brucella* OMP22 gene in urine, CSF, and blood samples was positive, confirming the diagnosis of NB (Supplementary Figure 1).

Anti-infective treatment was initiated on July 3 with rifampicin (600 mg IV once daily), doxycycline (100 mg orally twice daily), and trimethoprim-sulfamethoxazole (TMP-SMX; $800/160 \text{ mg orally}$ twice daily) (timeline in Figure 2). Within three days, his consciousness returned to normal, limb weakness improved, and body temperature normalized.

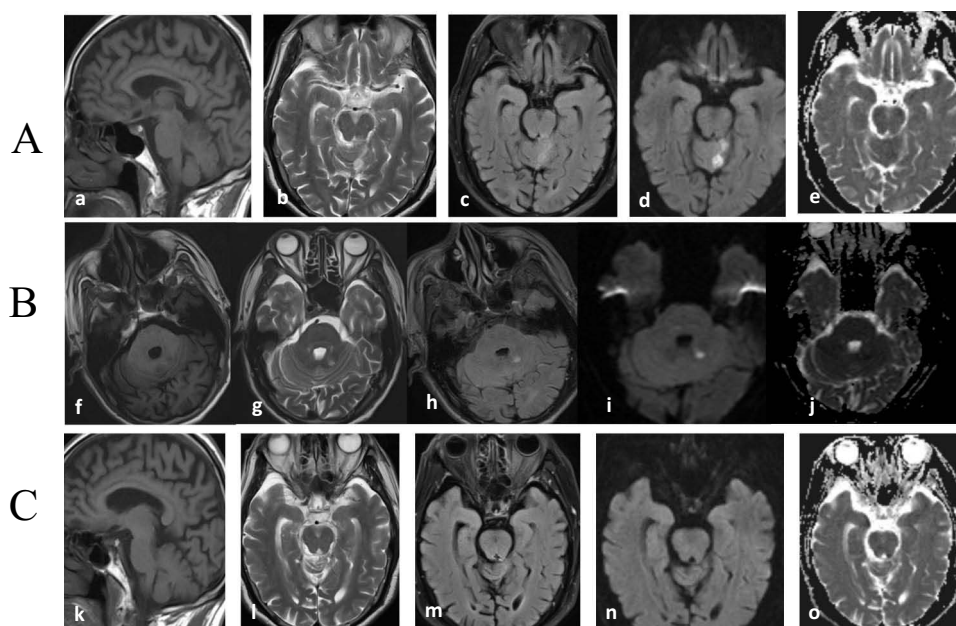


Figure 1 (A) On 25 June 2024, a 1.5T head MRI plain scan (a-e) revealed an acute infarct in the left cerebellar vermis, with striated hyperintensity on DWI (measuring approximately $2.5 \text{ cm} \times 1.0 \text{ cm}$), hypointensity on T1WI, hyperintensity on T2WI, and slightly hyperintensity on FLAIR, which was consistent with the manifestation of cytotoxic edema. The lesion was located in the blood supply area of the left posterior circulation. (B) The follow-up MRI (f-j) on July 2, 2024 revealed a $1.0 \text{ cm} \times 0.8 \text{ cm}$ patchy subacute infarction in the left cerebellar vermis, characterized by T1 hypointensity, T2/FLAIR hyperintensity and reduced DWI hyperintensity compared to the acute phase, demonstrating marked improvement. (C) On 4 December 2024, the patient came to the hospital for a follow-up. The previous infarct lesion in the left cerebellar vermis was not clearly visible on imaging (k-o) compared to earlier scans.

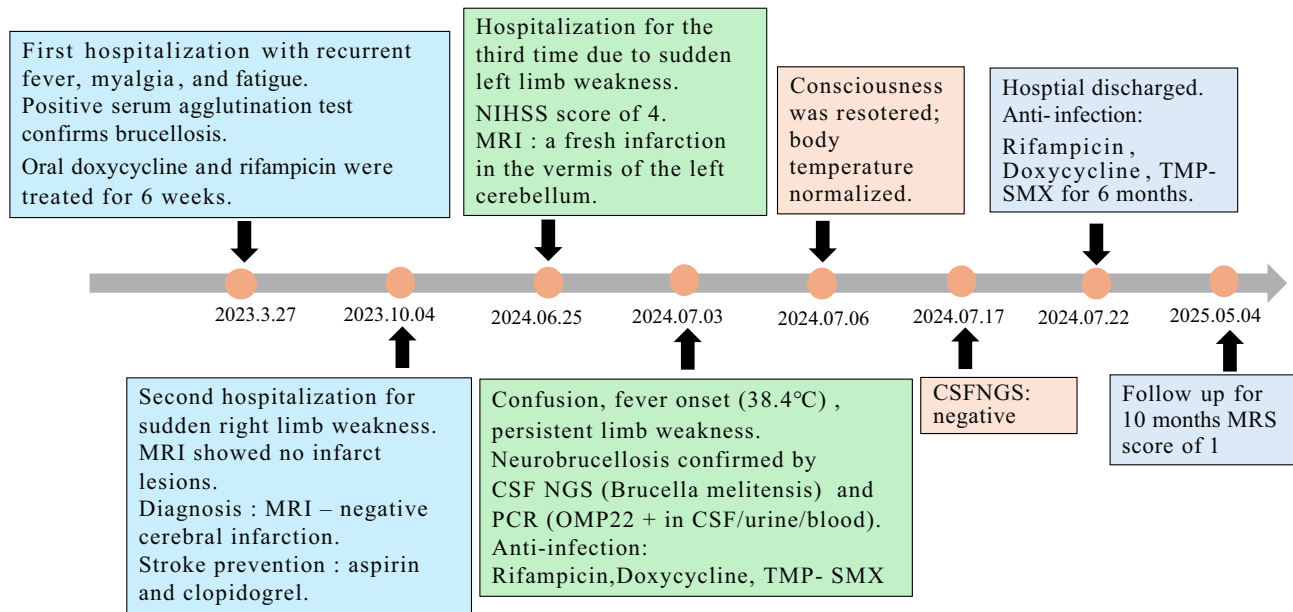


Figure 2 Timeline of this case report.

After two weeks of antibiotic therapy, CSF analysis (Table 1) showed a marked reduction in white blood cell count and protein levels compared to previous results, and repeat NGS returned negative. Following combination therapy with antibiotics, antiplatelet agents, lipid-lowering drugs, and circulation-enhancing medications, the patient was discharged. He was prescribed rifampicin (600 mg orally once daily), doxycycline (100 mg orally twice daily), and TMP-SMX (800/160 mg orally twice daily) for six months. Aspirin, clopidogrel, and atorvastatin were continued for secondary stroke prevention.

Follow-up evaluations at one week, five months, and ten months post-discharge demonstrated sustained remission, with normalized laboratory findings. At the five-month follow-up, MRI revealed no clear evidence of the prior infarct in the left cerebellar vermis (Figure 1). CSF analysis showed normal inflammatory markers, and NGS results were negative (Table 1). At the ten-month follow-up, the mRS score was 1. Continued follow-ups are scheduled every 3–6 months to monitor for recurrence and neurological sequelae.

Discussion

CNS involvement is a serious complication of brucellosis, with a highly heterogeneous clinical presentation.⁸ Neurological complications can occur at any stage of the disease, although diagnosis is typically made between 2 and 12 months after symptom onset.⁹ In retrospect, NB should have been strongly considered during the patient's initial hospitalization for limb weakness. This suspicion was warranted, given that the patient had completed a six-week treatment regimen but continued to experience intermittent fever. Moreover, despite taking aspirin and clopidogrel after

Table 1 Cerebrospinal Fluid (CSF) Parameters and Next-Generation Sequencing (NGS) Results During the Treatment Course

Date	WBC ($\times 10^6/L$) [0–8]	Protein (mg/L) [150–450]	Glucose (mmol/L) [2.5–4.5]	Chloride (mmol/L) [120–130]	NGS Result
2024-06-28	69 (↑↑)	2042.6 (↑↑)	2.38 (↓)	115 (↓)	<i>Brucella</i> spp. (1469 reads)
2024-07-16	28 (↑↑)	1025 (↑↑)	2.2 (↓)	118 (↓)	Negative
2024-12-04	3.8	474.7 (↑)	2.54	122	Negative

Note: ↑ indicates the index is higher than the reference range; ↑↑ indicates the index is significantly higher than the reference range; ↓ indicates the index is lower than the reference range.

discharge to prevent ischemic stroke, the patient suffered a second stroke. However, since the patient was admitted to the neurology department and failed to disclose his brucellosis history, the clinical team missed the opportunity to establish the association between NB and ischemic stroke during the diagnostic workup. Therefore, this case highlights the critical need to consider NB in the differential diagnosis of patients presenting with stroke-like symptoms in brucellosis-endemic regions. NB was ultimately confirmed during the second hospitalization through CSF NGS and PCR testing. The patient's symptoms improved significantly following combined antibiotic therapy, underscoring the importance of early diagnosis and timely treatment to achieve optimal outcomes.

The diagnosis of NB is based on consistent clinical findings along with direct or indirect evidence of *Brucella* in the CSF. Since cultures are positive in less than 25% of cases and conventional serological tests lack full sensitivity and specificity, molecular techniques have become valuable diagnostic tools in challenging cases.¹⁰ OMP22, a highly conserved outer membrane protein, serves as an immunodominant antigen for *Brucella*.¹¹ Martín-Martín et al¹² and Caro-Hernández et al¹³ demonstrated that *Brucella* strains lacking OMP22 exhibit attenuated virulence in mouse models and reduced invasiveness in host cells, underscoring its critical role in bacterial pathogenicity. Among molecular techniques, PCR is recognized as a highly useful tool for diagnosing many CNS infections and is considered the gold standard in some.¹⁴ Papadopoulos et al¹⁵ and Çiftci, A et al¹⁶ demonstrated that PCR assays exhibit higher sensitivity than serological tests in detecting brucellosis relapses, with CSF PCR offering faster and more sensitive detection compared to conventional microbiological methods. In this case, nucleic acids extracted from the patient's CSF, urine, and blood were amplified via PCR targeting the OMP22 gene, with a 526-bp fragment detected in all three specimens. These findings, together with NGS results, confirmed *Brucella* infection.

Treatment of NB remains controversial. Monotherapy is associated with relapse; therefore, combination therapy is recommended.⁸ The duration of treatment varies depending on patient response but generally lasts several months, often around 4–6 months or longer. Doxycycline is preferred among tetracyclines due to its superior tissue and CNS penetration and longer half-life.¹⁷ Arazi et al¹⁸ reported that ceftriaxone (83.2%), doxycycline (84.3%), and rifampicin (86.1%) were the most frequently prescribed antibiotics due to their proven CNS penetration, while TMP-SMX was used as adjunct therapy in 33.3% of cases. Notably, nephrotoxicity occurred in 7.9% of patients, emphasizing the need for careful therapeutic monitoring. Due to the patient's allergy to cephalosporins, this class of antibiotics was avoided. During hospitalization, the patient received doxycycline, rifampicin, and TMP-SMX, resulting in fever resolution and gradual neurological improvement.

When treating CNS infections, overcoming the blood-brain barrier (BBB) is essential for effective antibiotic delivery. Among the antibiotics mentioned, doxycycline and rifampicin readily cross the BBB, achieving therapeutic concentrations in the CSF, making them suitable choices for CNS brucellosis.¹⁹ TMP-SMX, which also penetrates the BBB, has been extensively used in NB. Although its role in uncomplicated brucellosis has been underappreciated, TMP-SMX is considered important as a third antibacterial agent in serious complications like NB. Streptomycin is generally avoided because of its poor CSF penetration and potential neurotoxic effects, which can complicate the clinical presentation.²⁰

Despite low mortality, neurological sequelae are common after NB. Erdem et al²¹ reported in the Istanbul study of 215 patients that one-fifth of treated individuals experienced permanent sequelae, with walking difficulties, hearing loss, and urinary incontinence being the most frequent residual disabilities. Although the patient completed a six-week antibiotic regimen following initial brucellosis diagnosis, the later development of NB indicates either initial treatment failure or insufficient therapy duration. Given the high relapse risk and prior treatment failure, an extended triple-antibiotic regimen of at least six months is strongly recommended. After six months of combined antibiotic therapy, the patient showed marked clinical improvement. At the ten-month follow-up, the mRS score was 1. Post-treatment, regular clinical follow-ups every 3–6 months are advised to monitor for relapse and neurological sequelae.

This case highlights the critical need to consider NB in the differential diagnosis of patients presenting with stroke-like symptoms in brucellosis-endemic regions. Notably, simultaneous amplification of the OMP22 gene fragment from the patient's urine, CSF, and blood samples was achieved, suggesting that urine-based detection may serve as a non-invasive diagnostic adjunct for early brucellosis diagnosis. Compared with conventional blood testing, urine-based detection offers several distinct clinical advantages: it provides a feasible alternative for patients with contraindications to invasive procedures; enables more practical large-scale sample collection and preservation in pastoral regions, thereby

being particularly suitable for brucellosis screening programs; and may potentially lead to reduced hospitalization duration and lower healthcare costs. Further research is planned to evaluate OMP22's diagnostic utility. Given the high recurrence rate of NB and the risk of relapse despite standard antibiotic regimens, combined antibiotic therapy with extended treatment duration is recommended to alleviate NB symptoms and improve clinical outcomes.

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 (KJ2024-541-02) approved the study.

Patient Consent for Publication

Written informed consent was obtained from the patient for the publication of this case report and accompanying images. Institutional approval for publication was not required.

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Author Contributions

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 this research was conducted without any commercial or financial relationships that could be perceived as a potential conflict of interest.

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