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CASE REPORT

# Confirmation of Tuberculous Meningitis Using Metagenomic Next-Generation Sequencing: A Case Report

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**Background:** Tuberculous meningitis (TBM) remains a significant clinical challenge due to limitations in traditional diagnostic methods, such as cerebrospinal fluid (CSF) analysis and tuberculosis culture, which often have long turnaround times and low sensitivity and specificity. This case report highlights the pivotal role of metagenomic next-generation sequencing (mNGS) in enhancing clinical knowledge for the diagnosis and management of TBM, supplementing insights into its clinical presentation and treatment.

**Case Presentation:** A 56-year-old male patient was admitted to the hospital with a chief complaint of "unconsciousness for 4 days". Following five days of antimicrobial therapy, the patient showed significant improvement with no fever or headache, but exhibited a suspicious left-sided Babinski sign (+). MRI revealed evidence of cerebral infarction, while spiral CT imaging showed hydrocephalus accompanied by interstitial cerebral edema. A lumbar puncture revealed elevated intracranial pressure, increased protein levels in CSF, reduced glucose and chloride concentrations, and negative results for CSF smear, CSF culture, and blood culture. T-SPOT testing was positive, and mNGS of CSF detected *Mycobacterium tuberculosis* (*M. tuberculosis*) Based on clinical and etiological findings, a diagnosis of tuberculous meningitis was confirmed. The patient was treated with quadruple anti-tuberculosis therapy combined with linezolid, resulting in clinical improvement. He was subsequently transferred to a specialized chest hospital for further management.

**Conclusion:** The patient's condition improved after 5 days of treatment. TBM is notoriously challenging to diagnose and treat. Traditional diagnostic methods, such as smear microscopy and tuberculosis culture, often yield low positive rates, delaying timely diagnosis and intervention. Early detection, accurate diagnosis, and prompt treatment are crucial for improving patient outcomes. mNGS of CSF has proven to be a powerful tool in TBM diagnosis, enabling early and precise identification of the pathogen, thereby facilitating timely treatment and reducing TBM-related mortality.

**Keywords:** tuberculous meningitis, metagenomic next-generation sequencing, diagnosis

## Background

Tuberculosis (TB) remains a significant global public health concern, ranking as the 13th leading cause of death worldwide and the second leading cause of infectious mortality. According to the 2023 World Health Organization Global Tuberculosis Report, approximately 10.6 million cases of TB were reported globally in 2022, including 6 million adult males, 3.4 million adult females, and 1.2 million children. India, Indonesia, and China accounted for the highest TB burdens globally.[1,2] Central nervous system (CNS) involvement occurs in approximately 10% of TB cases, primarily when *Mycobacterium tuberculosis* (*M. tuberculosis*) disseminates from the primary infection site (usually the lungs) into the bloodstream and spreads to the meninges. This can result in non-purulent inflammation, leading to tuberculous meningitis (TBM). Alarmingly, about 50% of

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TBM cases result in disability or death.[3–5] Traditional etiological diagnostic methods, such as acid-fast staining, are inexpensive, rapid, and simple to perform. However, their sensitivity is insufficient for detecting pathogens in samples with low bacterial loads. Similarly, CSF culture, while considered the gold standard, requires at least two weeks for results, limiting its utility for early diagnosis. The clinical manifestations of TBM are diverse and nonspecific, making it challenging to distinguish TBM from meningitis caused by other pathogens based solely on clinical and etiological findings.[3] Metagenomic next-generation sequencing (mNGS) has emerged as a powerful diagnostic tool for TBM, offering several advantages over conventional molecular methods such as GeneXpert, polymerase chain reaction (PCR), and line probe assay (LPA). While GeneXpert provides rapid detection with high specificity, its sensitivity remains suboptimal, particularly in CSF samples with low bacterial loads, and it is limited to detecting only specific genetic targets. PCR and LPA, though valuable, rely on preselected genetic targets, which can lead to false negatives due to genetic variability. In contrast, mNGS enables unbiased, hypothesis-free pathogen detection, improving diagnostic yield, especially in TBM cases where traditional methods produce ambiguous results.[6,7]

In this report, we present a case of TBM diagnosed through mNGS of CSF, bronchoalveolar lavage fluid (BALF), and blood. While previous studies have explored the use of mNGS in individual sample types, reports utilizing a comprehensive multi-sample approach remain limited. This case highlights the potential advantage of simultaneous testing of multiple body fluids, which may enhance diagnostic sensitivity, particularly when bacterial loads vary across different compartments. Additionally, mNGS facilitated early and accurate diagnosis, reinforcing its role as a complementary tool to existing molecular diagnostics.

## Case Presentation

The patient, a 56-year-old man, was admitted to the hospital on January 11, 2024, with a chief complaint of "unconsciousness for 4 days". His symptoms began on December 26, 2023, with high fever, headache, cough, and minimal sputum, which were initially overlooked. On January 3, 2024, he presented to another hospital with headache and dizziness, where MRI revealed bilateral frontal lacunar infarctions. He received symptomatic treatment, but specifics were unknown. Between January 6 and 9, he experienced recurrent coma episodes. A January 10 CT scan (Figure 1) from the referring hospital showed mild demyelination, multiple pontine infarctions, and periventricular white matter changes. During transfer to our hospital, he developed a 40°C fever and fell into a coma. His medical history included pancreatitis, cerebral infarction, gout, and renal insufficiency, with no known infections or significant medical interventions.

For further diagnosis and treatment, he was admitted to the emergency intensive care unit (EICU) with the possibility of "intracranial infection". A physical examination revealed a body temperature of 37°C, blood pressure of 153/89 mmHg, sedation, postural passivity, uncooperative abdominal and limb strength examinations, normal muscle tone, and physiological reflexes. A suspicious left-sided Babinski sign (+) was observed. A non-contrast CT scan of the head revealed generalized ventricular dilation, with marked prominence of the lateral and third ventricles, narrowing of

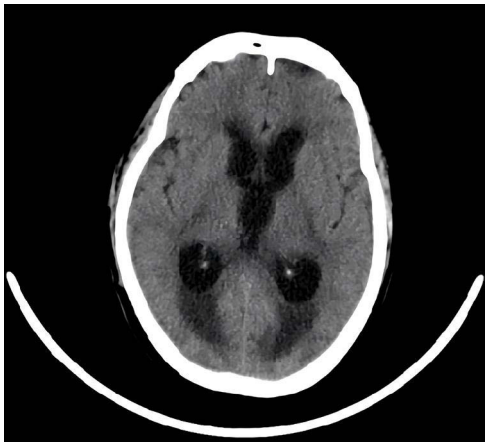

**Figure 1** CT image of the skull.

the sulci and fissures, and reduced density in the bilateral periventricular white matter, suggestive of hydrocephalus and interstitial cerebral edema. Chest CT revealed diffuse lung consolidations with small calcifications, raising suspicion of infectious lesions. Laboratory tests of CSF showed positive qualitative protein results, glucose 9.27 mmol/L, chloride 132.9 mmol/L, and trace total protein 10,728 mg/L. Smear results for sputum, CSF, and BALF were all negative for acid-fast bacilli.

Based on the patient's symptoms of confusion, fever, chills, elevated interleukin-6, and hypersensitive CRP levels, an intracranial infection was diagnosed. The patient was treated with Moxifloxacin sodium chloride injection (250 mL/day), meropenem injection (1000 mg every 12 hours), and concentrated sodium dehydration to temporarily alleviate clinical symptoms.

On January 13 (hospital day 3), blood mNGS identified *M. tuberculosis* complex group (240 reads), and BALF mNGS detected *M. tuberculosis* complex group (557 reads). These findings strongly supported a diagnosis of tuberculosis. A repeat lumbar puncture revealed CSF pressure exceeding 330 mmHg. Laboratory analysis of the CSF showed significant abnormalities, including protein qualitative test (+), elevated white blood cell count ($131.00 \times 10^6$/L), decreased glucose level (1.71 mmol/L), elevated chloride concentration (145.0 mmol/L), and markedly increased total trace protein (4373 mg/L). No cryptococci were observed on the smear. Following a consultation with specialists from the Chest Hospital, anti-tuberculosis therapy was initiated with the following regimen: isoniazid 0.6 g/day, rifampicin 0.45 g/day, ethambutol 0.75 g every two days, pyrazinamide 1.5 g every two days, linezolid 0.6 g every 12 hours, and dexamethasone 10 mg/day. That evening, the patient developed hydrocephalus with worsening intracranial pressure. Neurosurgery was urgently consulted, and an emergency ventriculoperitoneal shunt was performed to relieve the pressure.

On January 14 (hospital day 4), the CSF pressure was measured at 170 mmHg. CSF nucleic acid testing detected *M. tuberculosis* (+), and the mNGS analysis of CSF reported *M. tuberculosis* complex (11,265 reads) and *Pseudomonas aeruginosa* (10,423 reads). The Etiological Metagenomic Sequencing Detection Map of *M. tuberculosis* (Nm) is shown in Figure 2. The significantly higher sequence counts in the CSF compared to blood and BALF indicated a higher concentration of *M. tuberculosis* in the CSF, confirming a CNS infection and establishing a definitive diagnosis of TBM. Additionally, the detection of *P. aeruginosa* suggests a potential *P. aeruginosa* infection, providing a basis for further treatment adjustments. The treatment regimen was adjusted to include an intrathecal injection of dexamethasone (5 mg), an increased dose of meropenem (2000 mg every 12 hours), and concentrated sodium chloride injections (50 mL, three times daily). After five days of treatment, the patient showed significant improvement, with the resolution of fever and headache. On January 15 (the fifth day of hospitalization), the patient was transferred to the Chest Hospital for continued management. The overall pathogen identification process is summarized in Table 1.

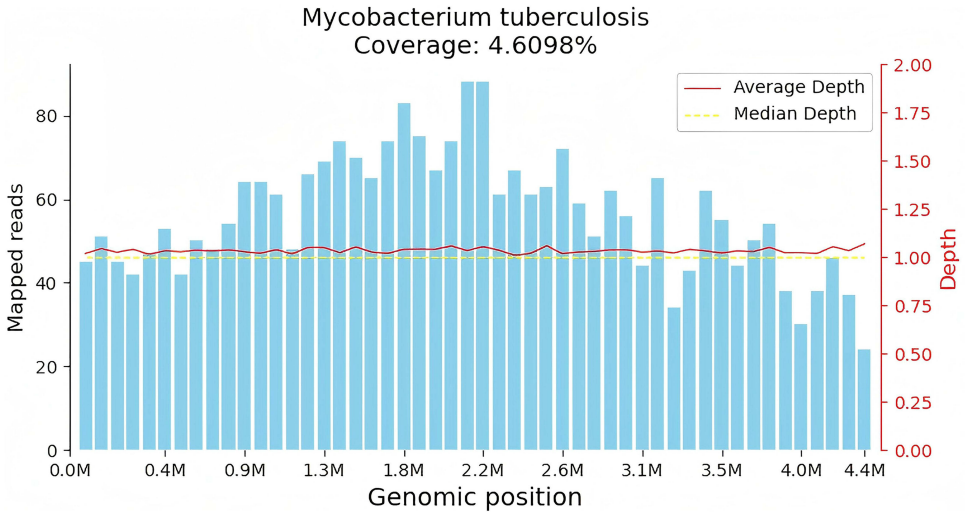


**Figure 2** Etiological Metagenomic Sequencing Detection Map of Mycobacterium tuberculosis (Nm).
**Notes**: The x-axis represents the genome size and location. The left y-axis indicates the number of sequenced reads aligned to the reference genome, while the right y-axis shows the alignment coverage of the sequenced reads to the reference genome.


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**Table 1** Pathogen Identification Results

| Testing Time (Date) | Jan 11, 2024 | Jan 12, 2024 | Jan 13, 2024 | Jan 14, 2024 | Jan 15, 2024 | Jan 16, 2024 |
|---|---|---|---|---|---|---|
| Smear | Sputum acid-fast smear: Negative; CSF acid-fast smear: Negative. | BALF smear: Negative. | | CSF acid-fast smear: Negative. | CSF acid-fast smear: Negative. | |
| Culture | | Blood culture: Negative | | CSF culture: Negative<br>BALF culture: Negative | | Blood culture: Negative |
| T-SPOT | | | | Blood test: Positive | | |
| mNGS Pathogen and Sequence Reads (n) | | | Blood mNGS: *M. tuberculosis* (240)<br>BALF mNGS: *M. tuberculosis* (557) | CSF mNGS: *M. tuberculosis* (11265)<br>*P. aeruginosa* (10,423 reads) | | |
| Others | | | | | Nucleic acid in CSF: *M. tuberculosis* | |

## Discussion and Conclusions

In this report, we describe the diagnosis and treatment of a male patient diagnosed with TBM through mNGS, and analyze the diagnostic and therapeutic experience based on the existing literature. Upon admission, the patient presented with a high fever, which was the main clinical manifestation. The diagnosis combined clinical and etiological methods, guided by the "2019 Guidelines for the Diagnosis and Treatment of CNS Tuberculosis in China". TBM was diagnosed based on the patient's persistent fever, headache, CSF examination, CT findings, and the patient's medical history and physical examination.

TBM typically arises when *M. tuberculosis* enters the CSF, often following the rupture of granulomas in other body parts, such as the medulla or subumbilicus. The infection can spread to the CNS via the blood vessels of the subarachnoid space, or from infection in nearby sinuses, such as the mastoid or sphenoid sinuses.[8,9] Meningeal enhancement on imaging is one of the most sensitive markers for TBM.[10] One of the most common complications in TBM patients is communicative hydrocephalus, resulting from basal cistern meningeal exudates obstructing the normal flow of CSF. In specific cases, tuberculomas or tuberculous abscesses can also block CSF flow, leading to noncommunicative hydrocephalus.[11] The diagnosis of TBM often relies on three typical clinical findings: basal cistern exudate, cerebral infarction, and hydrocephalus, collectively referred to as the diagnostic triad. In addition, TBM can lead to cranial nerve palsies, typically affecting the third, fourth, and sixth cranial nerves due to damage to blood vessels or cranial nerves enclosed in the basal exudates. However, due to the nonspecific and varied clinical presentation of TBM, symptoms can differ significantly among patients, and diagnosis is often made only after some degree of brain injury has occurred, complicating timely identification.[12,13]

Previous literature reports of TBM usually include fever, headache, impaired consciousness, cranial nerve damage, nerve localization and pathological signs, and this case is consistent with the literature report. The patient has persistent high fever and recurrent fever despite anti-infective therapy and is suspiciously positive for Babinski's sign on the left side. CT showed hydrocephalus with interstitial cerebral edema. Lumbar puncture manometry shows increased intracranial pressure, markedly elevated protein on cerebrospinal fluid assays, and decreased glucose and chloride homogenization. Lumbar puncture is important in differentiating different types of meningitis, and the combination of *M. tuberculosis* multiplication and metabolism and body response leads to characteristic changes in cerebrospinal fluid protein elevation and glucose and chloride decline.[14] In this case, CSF pressure is elevated, and CSF biochemistry and cytology show typical "elevated protein, low sugars and chlorides". Clinical findings, CSF examination, and CT scan can be used to diagnose and evaluate the condition clinically.

Traditional laboratory diagnostic methods, including smear tests and cultures, yielded negative results. However, the application of mNGS revealed significant advantages in this case. mNGS detected *M. tuberculosis* sequences in blood, BALF,

and CSF, with the highest read count observed in the CSF. This not only underscores the superior sensitivity of mNGS but also provides a quantitative assessment of pathogen load, particularly highlighting the elevated concentration of *M. tuberculosis* in the cerebrospinal fluid. Furthermore, mNGS identified a co-infection with *P. aeruginosa* in the CSF, a critical finding that informed the adjustment of the treatment regimen. This ability to detect and quantify pathogens, especially in complex cases involving mixed infections, is invaluable in guiding targeted therapeutic interventions and optimizing patient care.

The clinical symptoms of TB are often non-specific, necessitating a multifaceted approach to diagnosis that integrates knowledge and methodologies from diverse fields, such as etiology, pathology, molecular biology, and cellular immunology. Serological testing, including T-SPOT. TB and TB-Ab detection is commonly used in conjunction with other diagnostic methods to enhance the clinical accuracy of TB diagnosis, particularly for extrapulmonary tuberculosis (ex-TB) and pulmonary tuberculosis (TB). However, traditional assays such as PPD testing and TB-Ab may sometimes produce negative results, which could be influenced by factors like insufficient sensitivity, patient age, or an impaired immune response.[15,16] While histopathological examination (including smear tests for *M. tuberculosis*), PPD, and TB-Ab are routine diagnostic tools for TB, their positive detection rates are not always high, and negative results cannot entirely rule out TB. These tests should thus be considered as part of an auxiliary diagnostic framework rather than definitive indicators.[17] In this case, the inability to detect pathogenic bacteria in routine tests led to the use of mNGS, which successfully identified *M. tuberculosis* in the CSF and facilitated the initiation of anti-tuberculosis treatment. This underscores the critical value of mNGS in the accurate and timely diagnosis of tuberculosis.

Compared to traditional clinical diagnostic methods, mNGS offers a rapid and highly accurate approach for molecular diagnosis. mNGS serves as a powerful bioinformatics tool capable of characterizing a broad spectrum of pathogens, not only from laboratory cultures but also directly from clinical samples. This enables the detection of various pathogens, including viruses, bacteria, fungi, and parasites.[18] A key advantage of mNGS is its ability to swiftly identify emerging pathogens and novel variants of known pathogens, which is critical for early diagnosis and disease monitoring in infectious diseases.[19] Moreover, mNGS can detect known antimicrobial resistance genes and predict novel resistance gene variants. This provides valuable insights into the molecular mechanisms underlying drug resistance, disease transmission patterns, and pathogen virulence characteristics, making it an essential tool for monitoring and studying bacterial resistance.[20] With the ongoing advancements in NGS technology, the costs have significantly decreased, allowing NGS and tNGS to be integrated into tuberculosis control strategies.[21] TBM complicated by *P. aeruginosa* infection significantly increases treatment difficulty and mortality. The main challenges include limited therapeutic options, high antibiotic resistance, exacerbated inflammation, and severe neurological damage. Therefore, precise diagnosis, personalized combination therapy, and optimization of drug penetration are essential for improving prognosis. Future research should further explore the optimal combination treatment strategies, the clinical application of early mNGS-based diagnosis, and novel anti-infective approaches to enhance patient survival and reduce neurological sequelae.

TBM is associated with high rates of recurrence, disability, and mortality. To minimize these adverse outcomes, timely detection, accurate diagnosis, and appropriate treatment are essential. In this case, early identification and diagnosis were achieved through clinical evaluation, CSF analysis, and CT imaging, while mNGS was utilized to confirm the pathogen and ensure a definitive diagnosis. Thus, mNGS plays a critical role in the etiological diagnosis of infectious diseases, providing a more accurate and efficient approach for diagnosing tuberculosis and guiding treatment decisions. Future research on mNGS should prioritize cost-effectiveness analysis and large-scale validation to establish its clinical utility. Integrating mNGS into standard diagnostic workflows for TBM warrants further investigation to optimize sensitivity, specificity, and turnaround time. Additionally, advancing automation and standardized protocols could enhance its accessibility, reliability, and feasibility for routine clinical use.

## Consent Statement

Written informed consent for publication of this case, including any accompanying images, was obtained from the patient. This study was approved by the Ethics Committee of Guangdong Provincial People's Hospital (Approval No.: KY-N-2022003-03) and conducted in accordance with the Declaration of Helsinki. All research data were de-identified and analyzed anonymously. Additionally, the hospital has granted approval for the publication of this case.

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## Disclosure

The authors declare that they have no conflict of interest.

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