JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Utilizing metagenomic next-generation sequencing to diagnose central nervous system infections after craniotomy

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Abstract

Introduction: Postoperative central nervous system (CNS) infections in craniotomy patients diagnosed through clinical signs and cerebrospinal fluid (CSF) bacterial culture, pose a challenge due to the morbidity and mortality of bacterial meningitis. The objective of this study was to evaluate the clinical value of metagenomic next-generation sequencing (mNGS) in diagnosing CNS infections post craniotomy.

Methodology: A prospective study compared mNGS with traditional diagnostics from January 2021 to October 2023. Patients with suspected post-craniotomy intracranial infections were enrolled, following guidelines and regulations.

Results: mNGS and traditional culture diagnosed 111 patients with suspected intracranial infections. mNGS showed higher sensitivity (62.5% vs. 25%). Traditional culture excelled in specificity and positive predictive value. Of the 18 mNGS-positive samples, 12 were culture-negative. mNGS detected pathogens such as *Candida albicans* (2 cases), *Enterobacter cloacae* (1 case), *Enterococcus faecalis* (1 case), *Klebsiella pneumoniae* (2 cases), *Pseudomonas aeruginosa* (1 case), *Staphylococcus aureus* (2 cases), *Staphylococcus epidermidis* (2 cases), and *Streptococcus haemolyticus* (1 case). Some pathogens were likely missed due to prior antibiotic use and fastidious growth requirements. Physicians adjusted treatments based on mNGS pathogen detection for culture-negative patients. Empirical therapy continued for patients with negative results until more diagnostic information was available.

Conclusions: mNGS detects post-neurosurgery CNS infections, especially hard-to-cultivate microorganisms. While mNGS has advantages, traditional culture's higher positive predictive value confirms infections and remains indispensable. Combining mNGS with traditional methods provides a comprehensive diagnostic strategy, aiding physicians in accurately identifying infections, reducing misdiagnosis, and offering personalized treatment plans to improve outcomes and quality of life.

Key words: mNGS; CNS; postoperative; infection; meningitis.

J Infect Dev Ctries 2026; 20(2):263-270. doi:10.3855/jidc.21771

(Received 27 April 2025 – Accepted 30 July 2025)

Introduction

Many patients in the neurological intensive care unit (NICU) undergo craniotomy, and central nervous system (CNS) infections that may arise subsequently represent serious complications [1]. These infections commonly manifest postoperatively as meningitis, epidural abscess, subdural empyema, and brain abscess, among others [2–4]. They contribute to a substantial public health burden due to their association with high morbidity and mortality, often leading to permanent neurological deficits affecting motor skills, language, sensory perception, and cognitive function [5,6].

CNS infections can be classified as primary or secondary, with an overall reported incidence after neurosurgery ranging from 4% to 10%. The incidence of secondary CNS infections, such as brain abscesses, which are prevalent after neurosurgery, is now declining. The primary postoperative CNS infections include bacterial infections from open head injuries, cerebrospinal fluid (CSF) leakage, and various causes related to medical procedures [5]. Despite diagnostic efforts, a significant portion of postoperative CNS infections remain of unidentified etiology, presenting a challenge for management and treatment [7].

Managing CNS infections poses significant challenges due to limited diagnostic tools and the extensive range of potential differential diagnoses. This complexity makes the confirmation of suspected CNS infections challenging, underscoring the need for further research and advancements in diagnostic capabilities to improve patient outcomes. Given that diagnostic uncertainty often results in costly and ineffective treatments, there is an urgent need for innovative pathogen detection methods. Metagenomic next-generation sequencing (mNGS) offers a unique opportunity to address these challenges. Employing unbiased laboratory and computational techniques, mNGS involves unbiased sequencing of all nucleic

acids in a sample, followed by computational classification of reads to identify potential pathogens. This technique has been used to detect various pathogens, such as bacteria, fungi, protozoa, and viruses, in individuals with CNS infections [8–10]. mNGS is increasingly being used as a clinical diagnostic method, and criteria for testing for postoperative CNS infections have been described but not yet standardized.

Objectives

This study enrolled 119 patients with known or suspected CNS infections, in whom mNGS analysis of DNA samples was conducted to identify pathogens. The focus in the laboratory and analytical methods was on the detection of bacterial nucleic acids, as bacteria are the most commonly identified pathogens in postoperative CNS infections. The objective of this study was to evaluate the effectiveness of standard mNGS for identifying pathogens in postoperative CNS infections.

Methodology

Data sources and measurement

This prospective, single-center, observational cohort study was conducted at the NICU of Quzhou Affiliated Hospital of Wenzhou Medical University. Patients who underwent various neurosurgical procedures, including craniocerebral trauma, cerebral hemorrhage, aneurysm rupture, cerebral arteriovenous malformation (cAVM) excision, lumbar cistern drainage, ventricular drainage, brain tumor resection, and ventriculoperitoneal shunt surgery, were prospectively recruited by a surgeon at the institution from January 2021 to December 2023. All included patients provided informed consent. Patients younger than 18 years, those with insufficient clinical data, and those who refused lumbar puncture examination were excluded. All patients had CSF collected for analysis of nucleated cells, glucose, lactate, peripheral leukocytes, serum C-reactive protein, and leukocyte percentage. This study received approval from the Medical Ethics Committee (No. 2021-017) of the Quzhou Affiliated Hospital of Wenzhou Medical University.

Sample collection

A total of 12 mL CSF was aseptically collected from all patients via lumbar puncture or external ventricular drainage. Each sample was divided into two portions: 5 mL of CSF was inoculated into a BD BACTEC aerobic culture vial (Becton, Dickinson and Company, USA), and 5 mL of CSF was inoculated into a BD BACTEC anaerobic culture vial (Becton, Dickinson and Company, USA); 2 mL of CSF was reserved for mNGS. All samples were transported to the laboratory and processed within 4 hours of collection.

Microbiological culture

CSF specimens were homogenized and subjected to routine cultures for aerobic and anaerobic bacteria, fungi, and acid-fast bacilli. Half of the CSF was inoculated into aerobic blood culture bottles (BACTEC 9240 systemn (BD Diagnostics, Sparks, MD, USA), and the other half was inoculated into anaerobic blood culture bottles (BD Diagnostic Systems, Sparks, MD), which were then incubated in the BACTEC 9240 system (BD Diagnostics, Sparks, MD, USA). All samples were cultured for a standard period of 14 days. In the case of negative results, the incubation period was extended to 21 days. Positive culture results were analyzed to identify bacterial species. The cultivation results for each study subject were recorded, and appropriate negative controls were used for all procedures to mitigate the effects of contamination.

mNGS

The mNGS workflow included sample preparation, nucleic acid extraction, DNA library construction, metagenomic sequencing, and bioinformatic analysis. DNA was extracted from CSF using the TIANamp Micro DNA Kit (DP316; TIANGEN Biotech, Beijing, China). DNA libraries were prepared using the MGIEasy FS DNA Library Prep Kit (MGI Tech, China). Sequencing was performed on the BGISEQ-500 platform (BGI, Tianjin, China). Negative and positive controls of known pathogenic bacteria were used for the same batch of samples. In the case of evident contamination, the specimens were rechecked.

The clinical diagnosis was adjudicated by an expert panel using the predefined criteria.

Diagnosis of postoperative CNS infections

CNS infection diagnosis was divided into clinical diagnosis and etiological confirmation [11–14]. Clinical diagnosis was based on criteria 1–4, whereas etiological confirmation additionally required criterion 5.

1) Clinical diagnostic criteria: systemic inflammation, characterized by fever (> 38 °C) or hypothermia, high respiratory rate (> 20 breaths/min), and other manifestations of systemic infection; changes in consciousness and mental state, such as progressive decline in consciousness, drowsiness, lethargy, coma, fatigue, mental malaise, and delirium; symptoms and signs of increased intracranial pressure, including

headache, dizziness, nausea and vomiting, optic disc edema, and other typical manifestations; and meningeal irritation signs, such as neck resistance, Kirschner's sign, and positive Brinell's sign. Additional symptoms or signs may vary based on specific infection mechanisms, leading to different focal signs of dysfunction in various functional areas. Electrolyte imbalance, hydrocephalus, and pituitary dysfunction may also occur. Patients with ventriculoperitoneal shunts often exhibit signs of peritonitis, such as abdominal tenderness and rebound tenderness, while ventricular-thoracic shunt recipients may present signs of pleurisy.

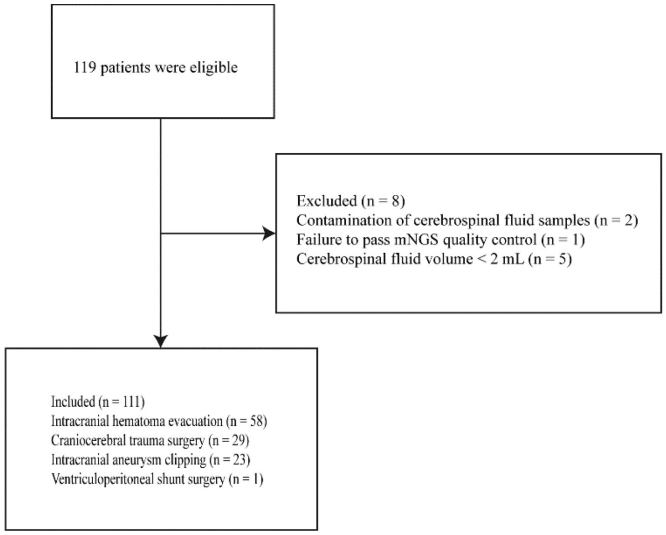
2) Blood-related signs: white blood cell count > 10.0×10^9/L, with a neutrophil proportion > 0.8.

3) Examinations related to intracranial pressure and CSF: intracranial pressure, where most patients with intracranial infection have a lumbar puncture open pressure > 200 mm H_2O; CSF appearing turbid, yellow, or purulent during the acute phase; CSF total of white blood cell count > 100×10^6/L and a neutrophil proportion > 0.7; and CSF biochemistry showing increased glucose content.

4) Imaging findings: Head computed tomography (CT) or magnetic resonance imaging (MRI) scans for meningitis lack specificity but often show diffuse brain edema, dural thickening, and strengthening. Ventriculitis may indicate a dilated ventricular system or the presence of a fluid level in the ventricles. Atypical brain abscess can exhibit ring strengthening in the brain as seen on CT and enhanced MRI.

5) Smear and culture: Smear and culture of CSF, incision secretions, drainage tubes, implants, and surgical specimens are crucial for diagnosis. Positive bacterial cultures of specimens, including smears, drainage tube heads, implants, and CSF, are considered the gold standard; however, contamination and colonization should be ruled out.

Figure 1. Flowchart of patient enrollment and exclusion.



Statistical analysis

A sample size determination was conducted to evaluate the efficacy of mNGS in detecting intracranial infections and compare it with traditional bacterial culture methods. Based on prior research findings and literature review, it was assumed that the efficacy of the NGS detection method would surpass that of traditional bacterial culture methods by 20% [8,15]. Accordingly, the two-sample Z test method was used for sample size calculation between two proportions. Before computing the sample size, the significance level ($\alpha = 0.05$) and statistical power ($1 - \beta = 0.80$) were determined. The success rate of the conventional testing method was estimated from previous relevant studies. Sample size calculation was performed using the professional statistical software PASS (v2023; NCSS, LLC, Kaysville, UT, USA). Upon inputting the aforementioned parameters, PASS generated the required sample size of 79. Considering a potential dropout rate of 20%, it was ultimately determined that 119 patients would be included in this study to ensure detection of the efficacy of the NGS detection method under the specified significance level and statistical power.

The sensitivity, specificity, and positive and negative predictive values of culture and mNGS were collected using clinical diagnosis and etiological confirmation as the gold standard. The Student's t test was used to assess differences in continuous variables between different groups; the Chi-squared test to evaluate differences in categorical variables; and the McNemar's test to compare differences in sensitivity, specificity, positive predictive value, and negative predictive value between the culture and mNGS methods. The Wilcoxon rank-sum test was used to compare various mNGS parameters. Statistical significance was defined as $p < 0.05$ (two-tailed). Statistical analyses were conducted using the SPSS software version 17 (IBM Inc., Armonk, NY, USA).

Results

Participants

The data of 119 patients were collected, among whom 8 patients were excluded: 2 due to contamination of CSF samples, 1 due to failure to pass mNGS quality control, and 5 due to inadequate collection of less than 2 mL of CSF from lumbar puncture. The remaining 111 patients, were included in the study (Figure 1). Twenty-

Table 1. Clinical information of the 111 cases included in the study.

Characteristic	Intracranial infections	Non-intracranial infections	*p*
Age	59.63 ± 12.44	66.06 ± 14.57	0.051
Gender (male/female)	11/13	57/30	0.099
Basal metabolic index (BMI)	25.27 ± 3.06	24.89 ± 3.73	0.059
Cerebrospinal fluid nucleated cell count	7307 ± 8463	206 ± 729	< 0.001
Cerebrospinal fluid lactate level	5.76 ± 2.32	3.62 ± 2.85	< 0.001
Cerebrospinal fluid protein concentration	5.87 ± 9.18	1.76 ± 4.54	< 0.001
Cerebrospinal fluid protein glucose level	1.49 ± 0.89	3.79 ± 0.80	< 0.001

four patients were classified as having intracranial infections based on clinical diagnosis and pathogen confirmation. Eighty-seven patients were classified as having non-intracranial infections (Table 1).

Descriptive data

There were no statistically significant differences in demographic characteristics, including age, gender, or body mass index (BMI), between the intracranial infections and non-intracranial infections groups. Regarding CSF indicators, there were statistically significant differences between the infection and non-infection groups in terms of nucleated cell count, lactate level, protein content, and glucose level. Among the CSF specimens of 111 patients suspected of having intracranial infection, 18 patients tested positive via mNGS, whereas only 6 patients tested positive via bacterial culture methods. Additionally, mNGS confirmed intracranial infection in 12 patients whose infection was not detected by conventional methods (Table 2). Six patients (5.4%) tested positive by both culture and mNGS. Ninety-three patients (83.8%) tested negative by both. Twelve patients (10.8%) tested negative by traditional testing methods but positive by mNGS. No patients tested positive by traditional testing methods and negative by mNGS (Figure 2).

Figure 2. Consistency between metagenomic next-generation sequencing and conventional methods.

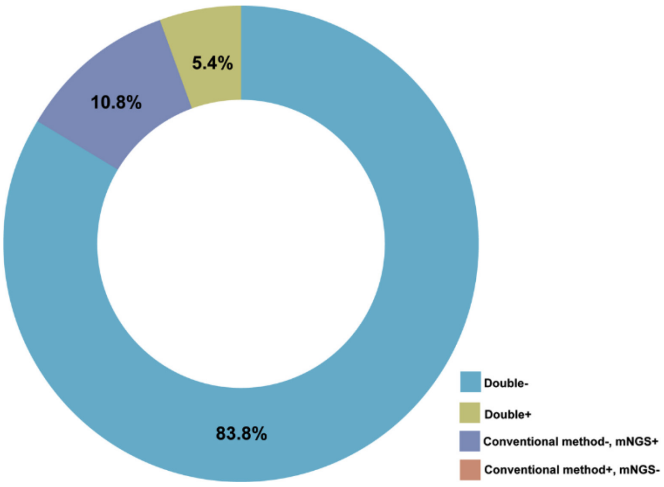


Table 2. The cerebrospinal fluid (CSF) metagenomic next-generation sequencing (mNGS) and CSF culture results were compared in 111 enrolled patients.

Culture	mNGS		
	Positive	Negative	Total
Positive	6	0	6
Negative	12	93	105
Total	18	93	111

Table 3. Comparing the performance of metagenomic next-generation sequencing (mNGS) and conventional methods in diagnosing bacterial infections of the central nervous system.

	Sensitivity	Specificity	Accuracy	Positive predictive value	Negative predictive value
Culture	25% (9.8%, 46.7%)	100% (95.8%, 100%)	83.4% (76.9%, 90.6%)	100% (54.1%,100%)	82.9% (74.3%,89.5%)
mNGS	62.5% (40.6%, 81.2%)	96.6% (90.2%, 99.3%)	89.2% (83.4%, 94.9%)	83.3% (58.6%,96.4%)	90.3% (84.3%,96.3%)
p	< 0.05	0.122	0.326	< 0.05	0.169

Using the final clinical diagnosis of intracranial infection as the gold standard, diagnostic outcomes of mNGS and conventional culture methods were classified as true positive (TP): tested positive with clinically confirmed infection; false positive (FP): tested positive without clinical infection; false negative (FN): tested negative with clinically confirmed infection; and true negative (TN): tested negative without clinical infection. Sensitivity (TP/(TP + FN) × 100%) reflects the ability to detect true infections, minimizing missed diagnoses and facilitating early treatment; specificity (TN/(TN + FP) × 100%) indicates the capacity to correctly exclude non-infections, reducing misdiagnosis and unnecessary antimicrobial therapy; accuracy ((TP + TN)/(TP + FP + FN + TN) × 100%) provides an overall measure of correct diagnoses among all cases; positive predictive value (PPV = TP/(TP + FP) × 100%) represents the probability that a positive result corresponds to a true infection, ensuring the reliability of positive findings and avoiding overtreatment; and negative predictive value (NPV = TN/(TN + FN) × 100%) denotes the likelihood that a negative result truly indicates absence of infection, bolstering confidence in negative findings and helping to rule out infection, thereby reducing unnecessary hospitalization and antibiotic use.

Outcome

The final clinical diagnosis of the presence or absence of intracranial infection was used as the gold standard, in the comparative diagnostic performance of mNGS and traditional culture methods. A total of 111 patients who had undergone cranial surgery and were suspected of having intracranial infection based on clinical symptoms were given empirical antibiotic treatment. In the end, 24 of them were confirmed to have intracranial infection. CSF samples from each patient were tested using both traditional bacterial culture and mNGS. Compared to traditional culture, mNGS had higher detection sensitivity (62.5% vs. 25%, $p < 0.05$), accuracy (89.2% vs. 83.4%, $p = 0.326$), and negative predictive value (90.3% vs. 82.9%, $p = 0.169$), with a particular advantage in sensitivity. Traditional bacterial culture was superior in specificity (96.6% vs. 100%, $p = 0.122$) and positive predictive value (83.3% vs. 100%, $p < 0.05$), especially positive predictive value (Table 3).

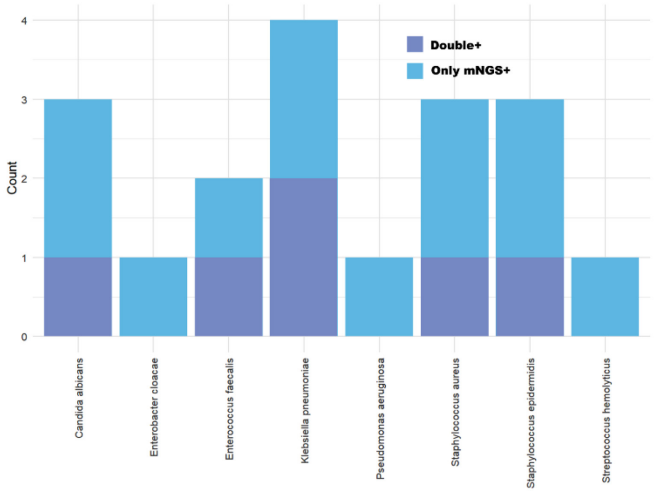
Pathogen detection results

The pathogens identified by both traditional culture and mNGS, along with their respective case counts, were *Candida albicans* with 3 cases, *Enterobacter cloacae* with 1 case, *Enterococcus faecalis* with 2 cases, *Klebsiella pneumoniae* with 4 cases, *Pseudomonas aeruginosa* with 1 case, *Staphylococcus aureus* with 3 cases, *Staphylococcus epidermidis* with 3 cases, and *Streptococcus haemolyticus* with 1 case (Figure 3).

Antimicrobial treatment

Physicians tailor the treatment plan in the clinical treatment of infectious diseases based on the results of pathogen detection. In the case of the 6 patients with positive cultures, doctors adjusted intravenous antimicrobial therapy according to the results of drug sensitivity testing to ensure that the medication was effective against the pathogen. When the culture results were negative but the mNGS results were positive, infectious disease specialists customized the antimicrobial treatment plan based on the mNGS findings. In the case of the patients with negative results from both culture and mNGS, the doctors might continue with empirical treatment, such as a broad-spectrum antimicrobial strategy using meropenem combined with vancomycin, until more diagnostic information became available. The entire treatment process requires dynamic adjustment, relying on the patients' response and further test results to ensure the appropriateness and effectiveness of the treatment plan.

Figure 3. Distribution of the detection rate.



Discussion

It is crucial to perform accurate and rapid pathogen detection and diagnosis for patients suspected of having intracranial infections after neurosurgery based on their clinical symptoms. Timely diagnosis can help doctors develop effective treatment plans, avoid potential serious complications, and even save patients' lives. In practice, the variety of pathogens, the complex and variable clinical presentations, and the fact that patients may have already received antibiotic treatment, all pose challenges to accurate pathogen detection [15,16]. The mNGS technology has shown potential in the diagnosis of primary CNS infections in a few studies [17,18], but a comprehensive assessment of its clinical diagnostic performance and added value in specific situations, such as after neurosurgical procedures including craniotomy for hematoma evacuation, external ventricular drainage, or V-P shunting, is still lacking. This study aimed to fill this research gap.

This study focused particularly on the additional diagnostic value of mNGS after empirical antibiotic treatment in patients with suspected postoperative intracranial infections. The purpose of this study was to directly evaluate the clinical efficacy of mNGS in diagnosing patients with postoperative secondary intracranial infections. To achieve this goal, clinical diagnosis was chosen as the gold standard for assessment rather than the results of traditional detection methods. This choice was made because all CSF samples were collected after suspected intracranial infections and empirical antibiotic treatment, a process that may reduce the diagnostic sensitivity of traditional culture methods. Clinical diagnosis may lack direct support from pathological evidence, but careful follow-up for more than 1 month can significantly reduce the risk of misdiagnosis [19,20]. Therefore, it is reasonable

to use clinical diagnosis as the reference standard when comparing different diagnostic methods. This study also aimed to explore the specific impact of mNGS results on clinical treatment decisions and how to integrate these molecular-level detection results with traditional clinical assessment and treatment practices to provide patients with more precise personalized treatment plans.

Through a systematic comparison between mNGS and conventional diagnostic methods, this study aimed to establish a stronger scientific foundation for the diagnosis and management of CNS infections, with the ultimate goal of enhancing clinical outcomes for patients. In this study, CSF samples tested by mNGS and traditional culture were systematically compared and analyzed. The results highlight several advantages of mNGS in the diagnosis of CNS infections. First, mNGS is significantly faster than traditional methods, with an average of only 2 days from sample collection to report issuance, while traditional methods require at least 2–5 days. This speed advantage makes rapid diagnosis and timely treatment possible, especially for acute infections, providing valuable time for clinical decision-making. In this study, mNGS had better sensitivity (62.5% vs. 25%, $p < 0.05$) than traditional culture, indicating its greater effectiveness in detecting pathogens, especially those that are difficult to cultivate by traditional methods. However, traditional culture showed higher accuracy in the positive predictive value (83.3% vs. 100%, $p < 0.05$), which may mean that traditional methods are still a reliable choice for confirming the presence of infection. These findings suggest that mNGS may be more effective in ruling out the possibility of infection, especially in complex or atypical infection cases. Traditional methods may provide more conclusive evidence for confirming the presence of infection. Therefore, the combined use of mNGS and traditional detection methods may provide a more comprehensive and accurate strategy for the diagnosis of CNS infections.

In this study, 6 patients were found to be infected with pathogens by traditional culture methods, while 18 patients were found to be infected with pathogens by mNGS technology. This difference was mainly due to the ability of mNGS technology to detect pathogens that are difficult to detect by traditional culture methods. Some pathogens may not grow or may grow very slowly under laboratory conditions, making them undetectable, while mNGS can directly detect the genetic material of these pathogens from clinical samples, providing a more comprehensive pathogen detection method.

A rigorous approach was adopted to ensure the accuracy of mNGS results. Strict thresholds were set, considering microbial sequences as true pathogens only when their abundance significantly exceeded background noise (e.g., negative controls) and reached preset reads per million (RPM) and reads per kilobase per million mapped reads (RPKM) limits. Each sequencing batch included negative controls (no template) and positive controls (known strains) to rule out contaminants. The candidates with ≥10% genome coverage, multi-segment distribution, and high alignment scores were prioritized. Furthermore, clinical evaluation was integrated by considering symptoms, imaging, inflammation markers, and antibiotic history to assess the pathogenic relevance of the detected microorganisms.

Another advantage of the mNGS technology is its ability to detect multiple pathogens simultaneously, including rare or fastidious microorganisms, which makes it highly sensitive for pathogen detection. However, this also brings certain challenges because mNGS may detect nonpathogenic microorganisms or the genetic material of dead bacteria in the samples, leading to false positives. These false-positive results need to be further verified by clinical judgment and other diagnostic information.

When mNGS and culture results conflicted, the clinical presentations, CSF white cell counts, protein levels, imaging, and medication history were reviewed to determine which result was more credible. Then, any potential issues during sample handling (e.g., prior antibiotics) or culture conditions (temperature, media) that could have caused false-negative cultures were checked, and the mNGS process for PCR inhibition or database matching issues were examined. Finally, a multidisciplinary team assessed the evidence, and adjusted the treatment plan or monitored dynamically to ensure diagnostic and therapeutic accuracy.

Therefore, in clinical practice, physicians should integrate the findings from both culture and mNGS with the patient's clinical presentation, medical history, and results from other auxiliary examinations to enhance diagnostic accuracy and develop the most effective treatment strategy. Through this comprehensive diagnostic approach, infections can be more accurately and quickly identified and treated, improving patient outcomes and quality of life.

Conclusions

mNGS technology has a significant advantage with respect to turnaround time in diagnosing CNS

infections after neurosurgery. It can provide test results quickly, which is crucial for the rapid diagnosis and timely treatment of acute infections. Furthermore, mNGS technology serves as a valuable adjunct to traditional culture methods, offering superior sensitivity, particularly in the detection of microorganisms that are difficult to cultivate using conventional approaches. While mNGS complements traditional methods, it does not replace them; instead, it enhances diagnostic capabilities by providing additional insights. This makes mNGS more effective at ruling out the possibility of infection, especially in cases that are complex or atypical.

Despite the outstanding performance of mNGS in certain aspects, traditional detection methods had a higher positive predictive value. This implies that traditional methods still hold irreplaceable value in confirming the presence of infection. Therefore, the combined use of mNGS and traditional detection methods may offer a more comprehensive and precise strategy for the diagnosis of CNS infections. Through this integrated diagnostic approach, physicians can more accurately identify infections, reduce the risk of misdiagnosis, and provide patients with more precise personalized treatment plans, thereby improving therapeutic outcomes and quality of life.

Ethics approval

This study was approved by the Medical Ethics Committee (No. 2021-017) of the Quzhou Affiliated Hospital of Wenzhou Medical University. Informed consent was obtained from all individual participants included in the study.

Consent for publication

Informed consent for publication was obtained from all individual participants involved in the study. The participants were provided with detailed information regarding the publication process, including the potential use of their data and the level of anonymity that would be maintained.

Funding

This work was supported by the Key Scientific and Technological Project of Zhejiang Province, specifically the Quzhou City Guided Project (Grant No. 2021022)

Availability of data and material

For inquiries regarding data access or further information about the study, please contact the corresponding author.

Authors contributions

JW, experimental and survey data collection; BJ, conceptualization, study design, original draft manuscript, supervision.

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Conflict of interest

No conflict of interest is declared.

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