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CASE REPORT

A Report of Primary Pyogenic Ventriculitis Caused by *Streptococcus Constellatus* Diagnosed by Metagenomic Next-Generation Sequencing

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Background: Primary ventriculitis is a rare but serious brain infection characterized by inflammation of the ependyma and purulence within the ventricular system. Due to the challenges in early diagnosis and the potential for suboptimal treatment, this condition carries a significant risk of complications such as recurrence, hydrocephalus, and death. Metagenomic next-generation sequencing (mNGS) enables the rapid and broad-spectrum identification of pathogens, facilitating timely and precise diagnosis.

Case Report: This study presents the first reported case of primary ventriculitis caused by *Streptococcus constellatus*. An 81-year-old female patient with hydrocephalus and clinical signs of central nervous system infection was diagnosed with primary ventriculitis based on brain magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis using mNGS. The patient underwent external ventricular drainage (EVD) and received a five-week course of ceftriaxone and linezolid. Following timely and targeted therapy, she demonstrated significant clinical improvement and was discharged without residual symptoms.

Conclusion: Key insights from this case include: 1) mNGS is an invaluable tool for the early and accurate diagnosis of primary ventriculitis; 2) MRI is indispensable for identifying characteristic radiological features of the condition; 3) prompt initiation and completion of appropriate antibiotic regimens significantly improve clinical outcomes.

Keywords: primary pyogenic ventriculitis, Streptococcus constellatus, metagenomic next-generation sequencing, mNGS

Background

Primary pyogenic ventriculitis, defined as suppurative inflammation within the ventricular system, is an uncommon but life-threatening condition.[1,2] Its rarity in adults and the nonspecific clinical presentation often lead to diagnostic challenges and delayed treatment, increasing the risk of poor outcomes such as hydrocephalus and mortality.[3] Early diagnosis of pyogenic ventriculitis and the identification of pathogenic bacteria are crucial for improving disease prognosis. Magnetic resonance imaging (MRI) is widely regarded as the most effective diagnostic tool for pyogenic ventriculitis.[2] According to published literature, common pathogens associated with pyogenic ventriculitis include *Neisseria meningitidis*,[4–6] *Staphylococcus aureus*,[7,8] and *Escherichia coli*.[2,9] Traditionally, cerebrospinal fluid (CSF) and blood cultures have been the primary methods for identifying causative bacteria. However, these techniques are time-consuming and often yield false-negative results, which can delay timely treatment. In contrast, metagenomic next-generation sequencing (mNGS) offers a rapid, unbiased, high-coverage, and reliable approach for pathogen detection.[10]

Here, we present the case of a patient admitted to the hospital due to fever. MRI identified ventricular encephalitis, and mNGS rapidly confirmed the presence of Streptococcus constellatus. Both MRI and mNGS provided crucial information for the diagnosis and appropriate antibiotic treatment of pyogenic ventriculitis.

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Metagenomic Second-Generation Sequencing Data Analysis and Case Reports

Metagenomic Second-Generation Sequencing Methods

With informed consent from the patient and their family, CSF samples were collected and stored in sterile cryopreservation tubes. The samples underwent broad-spectrum pathogen detection via mNGS using the MAPMITM system (CapitalBio MedLab Co. Ltd, Beijing) within 24 hours. Nucleic acids was extracted from 2mL CSF. For RNA, reverse transcription was performed to generate cDNA. Libraries were then constructed and sequenced using the BioelectronSeq4000 system (CapitalBio). The raw sequencing data were processed by quality filtering, removal of duplicate reads, and elimination of human genome sequences. The filtered reads were then aligned to the NCBI reference database for bacterial, archaeal, and fungal genomes, as well as DNA viruses infecting humans and bacteriophages.

Case Presentation

An 81-year-old female presented to our hospital with a primary complaint of fever (39 °C) accompanied by lethargy, unconsciousness, and limb weakness persisting for one day. Neurological examination revealed muscle strength graded as 4/5 in the upper limbs and 3/5 in the lower limbs, with no signs of meningeal irritation. Her medical history included hypertension for 10 years and coronary artery bypass graft surgery performed a decade prior. Additionally, she had a 10-year history of diabetes mellitus managed with metformin. Upon admission, her blood pressure was 160/115 mmHg.

A computed tomography (CT) scan of the brain revealed no significant abnormalities. However, diffusion-weighted magnetic resonance imaging (DWI-MRI) demonstrated hyperintense areas in the CSF located in the occipital horns of the bilateral ventricles (Figure 1A, indicated by black arrows). Correspondingly, T2-weighted MRI showed hypointense signals in the same regions (Figure 1B, indicated by black arrows). CSF analysis revealed elevated white blood cell count (0.07×10^9 g/L), L-lactate dehydrogenase (89 U/L), glucose (4.7 mmol/L), and protein concentration (2330 mg/L) (Table 1).

The routine CSF and blood culture yielded negative results.To further investigate the cause of the infection, we performed metagenomic next-generation sequencing (mNGS) on the CSF sample. Out of 13,064,186 quality-filtered sequencing reads, 7,705,191 were identified as human-derived, while 34,348 were classified as microbial. Among the microbial sequences, 2,362 were specifically mapped to *Streptococcus constellatus*. The genome coverage of *Streptococcus constellatus* was 11.91%, with an estimated DNA concentration of 5.82×10^2 copies/mL. Screening

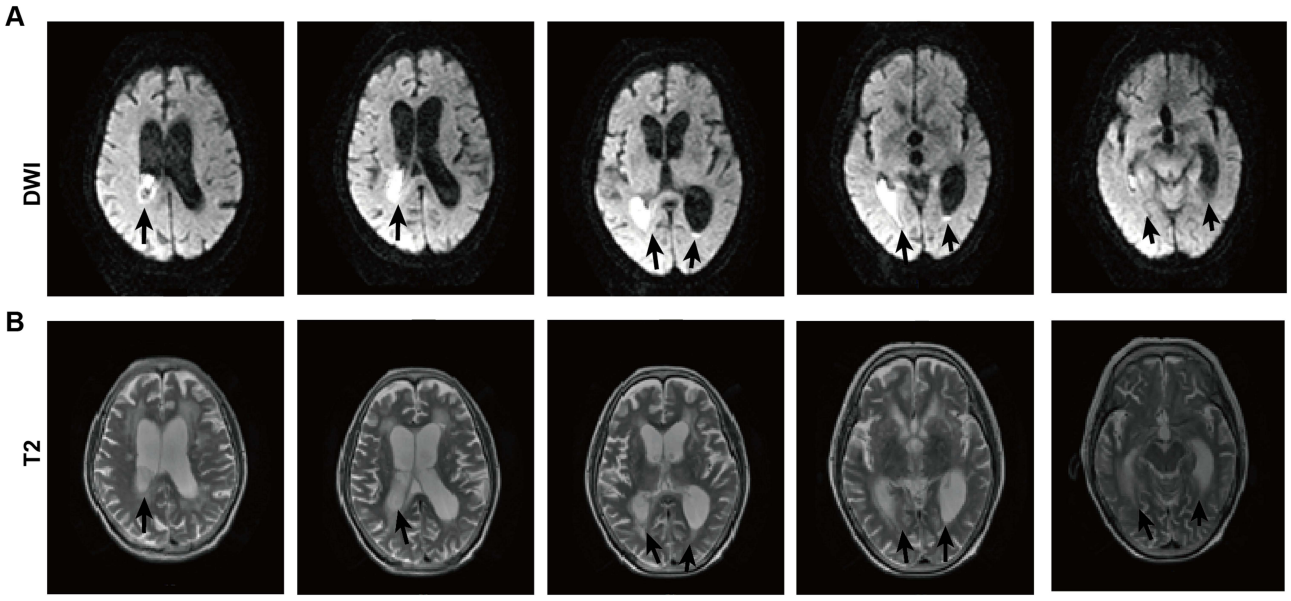

Figure 1 Brain magnetic resonance imaging (MRI) observations of the patients on admission. (**A**) Diffusion-weighted MRI (DWI-MRI) demonstrates hyperintense areas (indicated by black arrows) consistent with ventricular debris within the cerebrospinal fluid (CSF). (**B**) T2-weighted MRI reveals corresponding hypointense areas (indicated by black arrows) suggestive of ventricular debris in the CSF.

Table 1 Cerebrospinal Fluid Analysis

Variable	Reference Range	On Admission
Opening pressure (mmH_2O)	80–180	150
Aspect	Clear	Clear
Total protein (mg/L)	200–400	2330
Glucose	2.4–4.4	4.7
Cell count (x 10^9/L)	/	0.11
White cells (x 10^9/L)	0.000–0.010	0.070
L-lactate dehydrogenase (U/L)	3–40	89
Sodium (mmol/L)	136.0–145.0	145.1
Chloride (mmol/L)	120.0–132.0	116.3

results for other bacteria, fungi, and parasites were negative. Draft diagnostic reports were prepared by infectious disease specialists based on the patient's clinical presentation and additional laboratory findings. The mNGS analysis confirmed *Streptococcus constellatus* as the causative pathogen, leading to a diagnosis of *Streptococcus constellatus*-induced primary pyogenic ventriculitis (Figure 2).

Upon the identification of the causative strain of the ventricular infection, the patient promptly received intravenous treatment with ceftriaxone (2.0 g once daily) and linezolid (300 mg every 12 hours) for a period of 30 days. An external ventricular drain (EVD) was also inserted into the right lateral ventricle to facilitate the drainage of purulent material. Over the course of her treatment, the patient's fever subsided and her mental status significantly improved. She was discharged after completing the 30-day treatment regimen. Follow-up two months post-discharge revealed no indications of residual infection. As of the time of this report, the patient remains bedridden but shows no signs of recurrent infection.

Discussion and Conclusions

We describe a case of primary pyogenic ventriculitis caused by *Streptococcus constellatus*, diagnosed using MRI and mNGS. Pyogenic ventriculitis, a purulent infection of the cerebral ventricles, is often associated with meningitis, ruptured abscesses, or infections related shunts or catheters.[11] Primary pyogenic ventriculitis, however, is infrequently reported. Prior to this report, primary pyogenic ventriculitis had been attributed to various pathogens, including *meningitidis*,[4–6] *Staphylococcus aureus*,[7,8] and *Escherichia coli*,[2,9,12] among others. Diagnosis in these cases typically relied on MRI imaging combined with CSF and blood cultures. To our knowledge, this is the first reported case of primary pyogenic ventriculitis caused by *Streptococcus constellatus*.

Pyogenic ventriculitis is frequently misdiagnosed as meningitis or encephalitis due to overlapping clinical symptoms, such as headache, fever, seizures, focal neurological deficits, neck stiffness, and altered consciousness.[2] Notably, signs of meningeal irritation are typically absent in cases of pyogenic ventriculitis. Our patient presented with high fever,

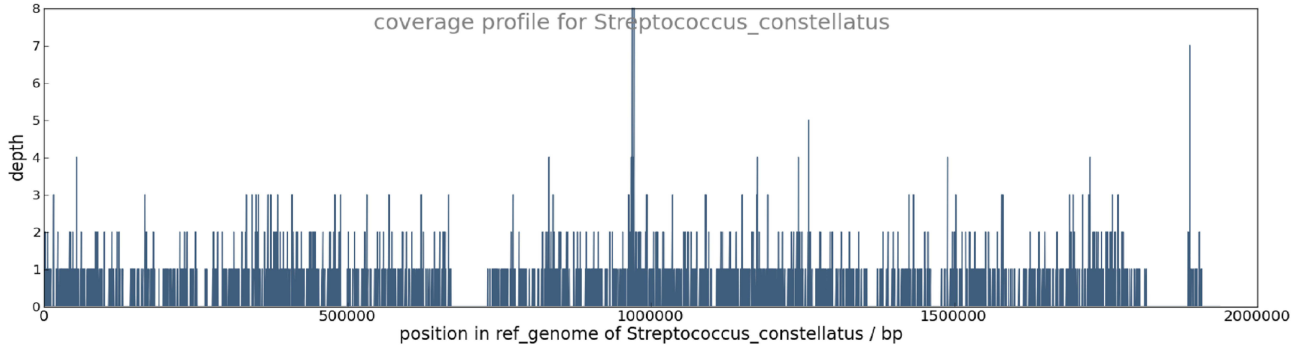

Figure 2 The metagenomic next-generation sequencing (mNGS) analysis of cerebrospinal fluid from the 81-year-old patient. The mNGS analysis identified 34,348 microbial sequences, with 2,362 reads specifically mapped to Streptococcus constellatus. These reads accounted for 11.91% (230,977/1,928,846) of the organism's genome coverage.

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confusion, limb weakness, and vomiting. MRI, the most sensitive diagnostic tool for pyogenic ventriculitis revealed characteristic features, including periventricular hyperintense signals, ependymal enhancement, and hydrocephalus.MRI, the most sensitive diagnostic tool.[13] For pyogenic ventriculitis revealed characteristic features, including periventricular hyperintense signals, ependymal enhancement, and hydrocephalus. CSF analysis showed elevated white blood cell counts and protein levels, consistent with infection and purulent inflammation. Early diagnosis and precise pathogen identification are crucial for initiating appropriate treatment and improving outcomes.

Streptococcus constellatus is a subspecies of the *Streptococcus anginosus* group (SAG), formerly referred to as the *milleri group*, which was first described by Guthof in 1956 during the isolation of bacteria from dental abscesses.[14] Although part of the normal human microbiota, *Streptococcus constellatus* has been increasingly recognized as opportunistic pathogens capable of causing multi-organ infections and abscess formation.[15] Risk factors for SAG-related infections include malignancies, type 2 diabetes mellitus, central nervous system involvement, chronic kidney disease, chronic respiratory disease, viral hepatitis, and connective tissue disorders.[16] S. constellatus is closely associated with dental plaque and periodontal disease and has been isolated from various infections, including bacteremia, peritonsillar abscesses, orofacial abscesses, pleural empyema, pneumonia, endocarditis, and liver abscesses.[14] However, to date, no reports have reported *S. constellatus* as a causative agent of primary pyogenic ventriculitis.

Bacterial entry into the brain can occur through hematogenous dissemination, direct extension, or post-traumatic/post-surgical routes. In this case, the patient's 30-year history of hypertension, 10-year history of diabetes, and prior coronary artery bypass graft surgery (performed 10 years ago) collectively increased the risk of *Streptococcus constellatus*-induced pyogenic ventriculitis. While the graft could rarely serve as a bacterial colonization site, the patient's underlying conditions and advanced age are more likely to have contributed to immune dysfunction and infection susceptibility. *Streptococcus constellatus* may contribute to infection through mechanisms such as biofilm formation and immune evasion, which play a significant role in the pathogenesis of ventriculitis. *Streptococcus constellatus* contributes to infection through multiple mechanisms, including biofilm formation, which enhances its ability to adhere to tissues and resist immune clearance. It produces capsular polysaccharides and proteases to evade host immune responses, and secretes toxins and enzymes (eg, hemolysins and hyaluronidase) that promote tissue invasion and inflammation. These virulence factors collectively enable its survival, dissemination, and pathogenicity in susceptible hosts. Recent reported case documented meningitis and ventriculitis caused by *Streptococcus intermedius*, another member of the SAG.[17] *Streptococcus intermedius* possesses virulence factors, such as antigens I/II surface proteins, hyaluronidase, and a polysaccharide capsule, which may contribute to its ability to cause central nervous system (CNS) infections, including brain abscesses.

The identification of the SAG and its role in infectious diseases remains challenging due to the lack of a standardized diagnostic method. Traditional cultivation techniques and biochemical tests demonstrate limited accuracy in identifying SAG.[18] Traditional methods, such as cerebrospinal fluid (CSF) and blood cultures, have been the primary diagnostic tools. However, these conventional approaches are time-consuming and may delay the identification of the causative organism. Molecular methods, such as PCR targeting specific sequences (eg, *groESL, polymorphisms*, and *ily*), and mass spectrometry, particularly MALDI-TOF-MS, have been developed to improve identification. Among these, mNGS stands out as the most promising diagnostic approach due to its high-throughput capability and rapid turnaround time. mNGS provides critical information for clinical diagnosis and guides appropriate antimicrobial therapy in complex infectious diseases. The integration of advanced imaging modalities, such as MRI, with mNGS enables faster and more accurate diagnosis, facilitating the identification of causative pathogens in conditions like pyogenic ventriculitis.

Early initiation and completion of an appropriate antibiotic regimen are critical for improving prognosis in patients with pyogenic ventriculitis. Wang et al reported a case of recurrent primary pyogenic ventriculitis caused by *Escherichia coli*.[9] Notably, changes in CSF parameters may not accurately reflect the severity of the infection, as the primary site of infection in pyogenic ventriculitis is the ventricles. Sole reliance on CSF analysis can result in residual infections, particularly in the choroid plexus, which may act as a reservoir for recurrent episodes.[9] In cases where the efficacy of ceftriaxone is inadequate, timely implementation of EVD is essential to manage the condition effectively.

In conclusion, we present a case of pyogenic ventriculitis caused by *Streptococcus constellatus*, diagnosed through a combination of MRI and mNGS. This case highlights the utility of mNGS as a powerful diagnostic tool for the early identification of causative pathogens and the accurate diagnosis of primary ventriculitis. Prompt diagnosis, timely

initiation of treatment, and completion of a full course of appropriate antibiotics are critical for effective disease management and improved patient outcomes.

Ethics and Consent

The waiver of ethic review in publications of photograph and medical records in single-case report is comply with the Declaration of Helsinki and was approved by the Medical Ethics Committee, The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology. According to patient data confidentiality principle, the patient's written informed consent was obtained for publications of all the images and case details.

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.

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.

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