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CASE SERIES

A Report of Two Cases of Meningoencephalitis Caused by *Streptococcus intermedius*

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Objective: In this paper, we analyzed the clinical data of patients with meningoencephalitis caused by *Streptococcus intermedius* to understand better the clinical characteristics of the disease and recommend auxiliary diagnostic mode as well as treatment experience.

Methods: We reviewed the clinical data of two patients admitted to our department in 2019 with meningoencephalitis caused by *S. intermedius*.

Results: Two female patients were examined, one of whom had a history of radiotherapy for nasopharyngeal carcinoma while the other had no underlying disease. These two patients were admitted with symptoms of meningoencephalitis. Cerebrospinal fluid examinations revealed elevated levels of leukocytes and protein. After treatment with meropenem, the condition improved for a brief time, but then worsened with a decline in mental status and limb movement. Blood and cerebrospinal fluid cultures demonstrated the absence of pathogenic bacteria, while genome sequencing of cerebrospinal fluids revealed the presence of *S. intermedius*. Cranial magnetic resonance imaging revealed multiple cerebral abscesses (CAs). After coadministration of linezolid as an anti-infective, clinical symptoms gradually improved, and the CAs shrank on follow-up imaging. The condition exhibited a pattern of improvement-deterioration-improvement.

Conclusion: Meningoencephalitis caused by *S. intermedius* is complex and prone to fluctuation and formation of multiple CAs. The definitive clinical diagnosis of this disease can be aided by genome sequencing technology, and early clarification of the etiology combined with the use of potent antibiotics is effective.

Keywords: Genome sequencing, meningoencephalitis, multiple cerebral abscesses *Streptococcus intermedius*

Introduction

Streptococcus intermedius belongs to the *Streptococcus anginosus* group and is a type of Gram-positive microaerophilic bacteria that affects people of all ages, from infants to the elderly, worldwide.[1] *S. intermedius* infections are typically subacute in nature, and generally do not cause bacteremia and are predisposed to the development of cerebral abscesses (CAs). *S. intermedius*, which is part of the flora of the oral cavity, pharynx, and gastrointestinal tract, can secrete proteolytic enzymes, destroy tissues, and lead to the formation of localized abscesses. When the immune system is compromised, the risk of infection with *S. intermedius* and subsequent development of severe CAs are significantly increased.[2–5] *S. intermedius* is one of the most prevalent pathogens of brain, liver, and chest abscesses, and thus increases morbidity and mortality in patients. Although numerous cases of *S. intermedius* infections have been reported, it remains understudied relative to other members of the *S. anginosus* group.

In this paper, we analyzed the clinical manifestations and laboratory results of two patients admitted to our department in 2019 with meningoencephalitis caused by *S. intermedius* to enhance the clinical knowledge of the disease and diagnosis and treatment experience.

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Case Information

Case Presentation of Patient 1

A 71-year-old Han ethnicity woman was admitted to the hospital on May 26th, 2019, with "fever for four days and altered mental status with two days of limb weakness". One day prior to admission, a lumbar puncture was performed at a different hospital, which demonstrated a pressure of 280 mmH2O and the cerebrospinal fluid (CSF) contained more than 3000 leukocytes that were predominantly multinucleated and had significantly elevated protein levels. Physical examinations revealed clear consciousness, unclear articulation, grade 3 muscle strength in the right upper limb, and neck resistance. Magnetic resonance (MR) enhancement suggested multiple nodular lesions in the bilateral cerebral and cerebellar hemispheres and the region of the basal ganglia (Figure 1). The patient was diagnosed with multiple CAs and ceftriaxone was administered as an anti-infective. The patient developed a fever again on the third day, accompanied by a worsening headache, dysphoria, speechlessness, and decreased limb movement. After increasing the antibiotic to meropenem, the fever subsided, but dysphoria, limb weakness, and speechlessness persisted. Cerebrospinal fluid culture revealed no fungi or bacteria, At the same time, high-throughput sequencing technology was used in cerebrospinal fluid samples, and the total number of sequences detected was 12,324,269, of which human sequences accounted for 96.83%, and the total number of microbial sequences detected was 1171, which excluded suspected microorganisms infection and confirmed the presence of streptococcus intermedius.MR enhancement on June 6th revealed numerous ring-enhancing lesions in both cerebral and cerebellar hemispheres (Figure 2). The symptoms improved after one month of additional anti-infection treatment with linezolid, and normal speech and limb movements had been restored. When the condition of the patients was at its most severe, a small dose of hormones were used to reduce the inflammatory response for a brief period of time. On June 29th, imaging follow-up revealed a significant reduction in brain swelling lesions (Figure 3). The patient is conscious and has normal limb movement without convulsions, but the overall response is slow with hypomnesis. The cerebrospinal fluid and imaging results are summarized in Table 1 and Figures 1–3.

Case Presentation of Patient 2

A 53-year-old Han ethnicity woman was admitted to the hospital on July 26th, 2019 for "three days of headache, dizziness, and vomiting". Several years ago, she had been treated for nasopharyngeal cancer with radiotherapy, leaving her with residual barylalia, hearing loss, and skin lesions on the back of the neck. Regular review revealed no recurrences. Physical examinations

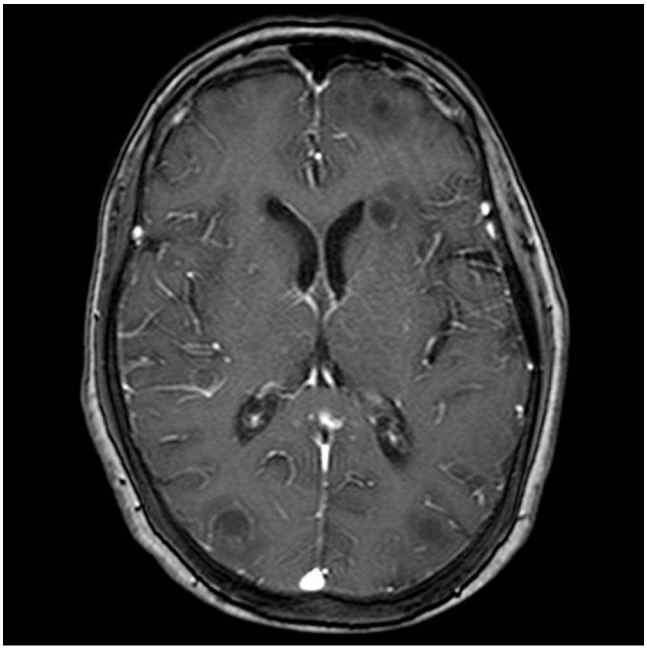

Figure 1 MR findings on May 26: Multiple nodular lesions were observed in the bilateral cerebral, cerebellar, and basal ganglia regions, accompanied by peri-lesion edema and mild ring enhancement.

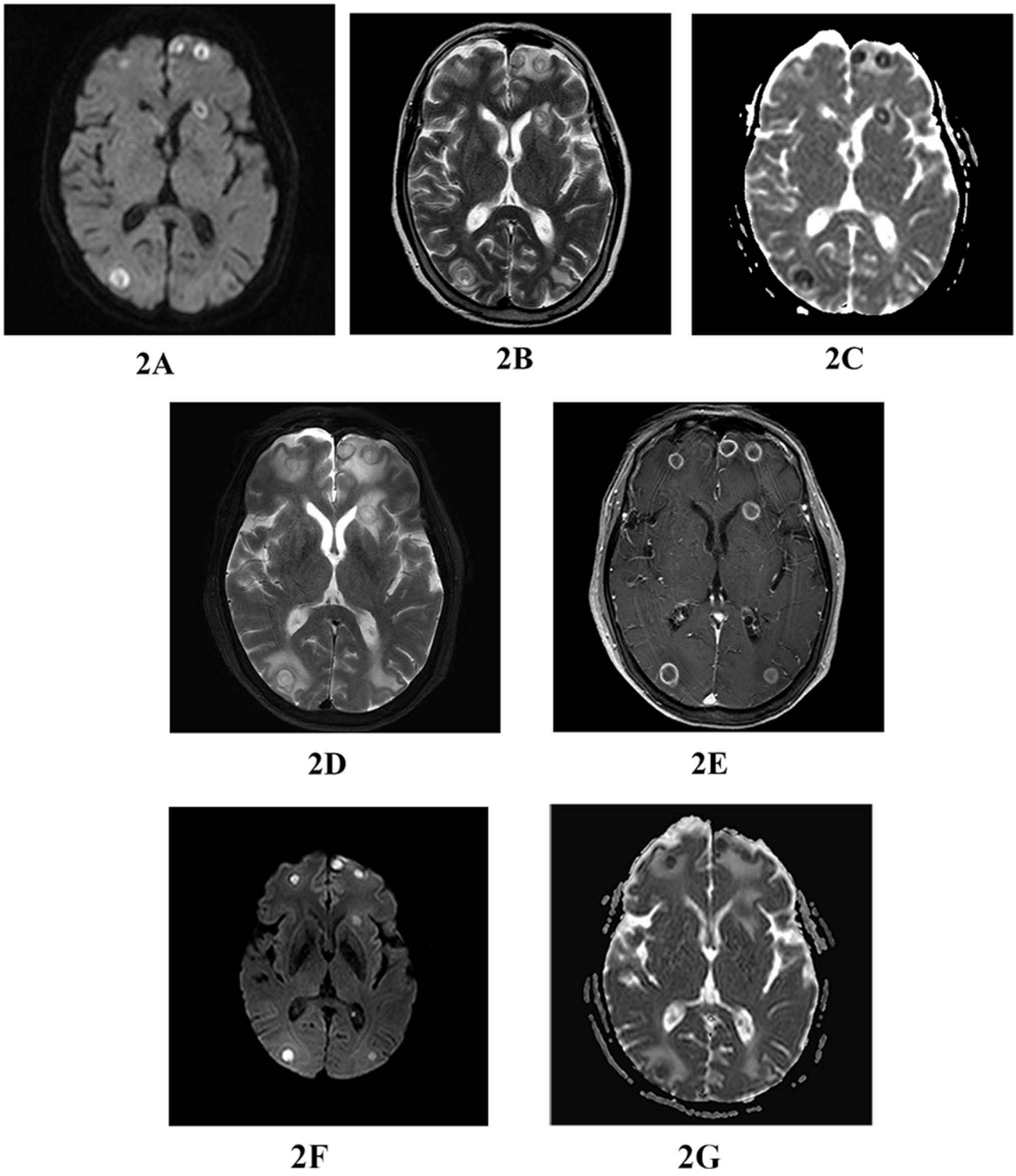

Figure 2 MR enhancement on June 6: Multiple ring-enhancing lesions were observed in bilateral cerebral and cerebellar hemispheres, along with perifocal edema and a uniform and smooth lesion ring wall. Pseudocontinuous arterial spin labeling (pCASL) and dynamic susceptibility contrast-enhanced perfusion-weighted imaging (DSC-PWI) demonstrated that the ring-enhancing lesions (solid portion) were hypoperfused, whereas diffusion-weighted imaging (DWI) demonstrated that diffusion was not obviously restricted, with most of the necrotic and liquefied areas within the lesion being significantly restricted in diffusion. Magnetic resonance spectroscopy (MRS) revealed a prominent lip peak in the lesion, along with diminished NAA, Cr, and Cho peaks, particularly the NAA and Cr peaks. (**A**) DWI sequence shows multiple nodular lesions in bilateral cerebral hemispheres, with low signal in the center of the lesion and high signal around it. (**B**) T2 sequence shows multiple nodular lesions in bilateral cerebral hemispheres with peripheral edema. (**C**) ADC sequence showed multiple nodular lesions in bilateral cerebral hemispheres, with high signal in the center of the lesion and low signal around it. (**D**) T2 sequence shows multiple nodular lesions in both cerebral hemispheres. (**E**) T1 enhanced scans showed multiple nodular lesions in both cerebral hemispheres, with ring-enhancement. (**F**) Multiple nodular high signal lesions in bilateral cerebral hemispheres of DWI sequence. (**G**) The ADC shows multiple nodular lesions in both cerebral hemispheres with low signal and restricted diffusion.

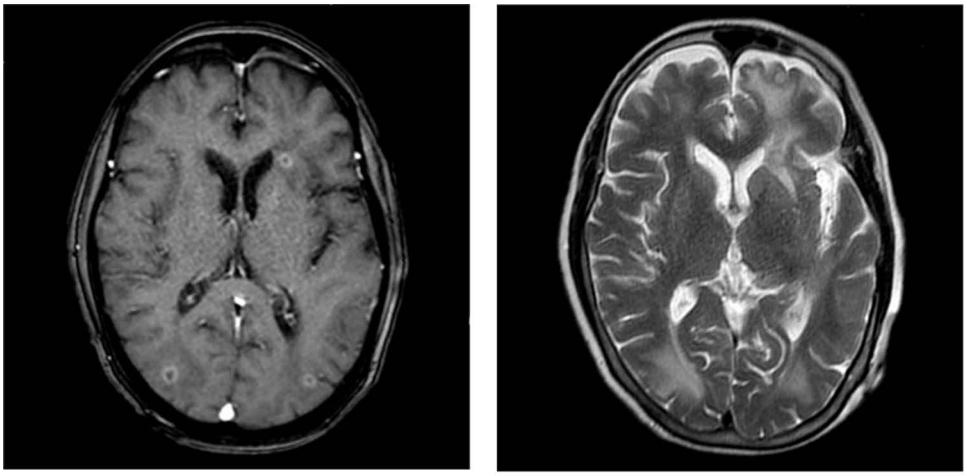

Figure 3 MR on June 29: multiple ring-enhancing lesions were still found in the bilateral cerebral and cerebellar hemispheres, which had shrunk significantly. (**A**) T1 enhancement sequence showed multiple circular enhancement lesions on both sides of the brain, marked perifocal edema, uniform, smooth ring wall, and ring-enhancement. (**B**) The T2 sequence shows that the lesion has a high signal, with significant surrounding edema.

indicated marked neck resistance and a leukocyte count of 13.64 × 10^9/L. The patient's condition worsened on the second day of admission, accompanied by deteriorating mental status, frequent vomiting, signs of apathy, speechlessness, and decreased limb movements. Cranial MR enhancement revealed strip-shaped fluid signals adjacent to the cerebral falx and tentorium cerebelli on July 28th (Figure 4). Lumbar puncture pressure was elevated, and the cerebrospinal fluid leukocytes were 1022 x10^6/L, 88% of which were monocytes, and the protein was also high and the sugar was low. The patient was diagnosed with purulent meningitis and given anti-infective meropenem. On the 5th day of admission, the patient's mental status improved and she was able to walk a short distance with assistance—there was no vomiting or fever and her speech improved. The patient's symptoms worsened on August 8th with recurrent vomiting, decreased movements of the right lower limb, and intermittent paraphasia. The cerebrospinal fluid bacterial culture result was negative. Pathogenic bacteria in the cerebrospinal fluid were sequenced using the metagenome DNA sequencing method, and 853 sequences indicating the existence of *S. intermedius* were detected. Additional linezolid was administered as an anti-infection medication. On August 13th, cranial MR findings revealed multiple abnormal signals in the left frontoparietal lobe, the corpus callosum splenium, and the left temporal pole (Figure 5). As the family of the patient refused surgical incision and drainage, meropenem and linezolid were continued as an anti-infection regimen. The patient's symptoms improved over the course of one week, including a decrease in headache and neck pain, a decrease in vomiting, and an increase in

Table 1 Cerebrospinal Fluid Results of Patient 1

Time	May 25	May 31	June 12	July 10	Reference value
Pressure (mmH2O)	280	110	100	90	80~180
Leucocyte count (×10^6/L)	More than 3000	236	3	10	0~5
Leucocyte percentage	Mostly multinucleated cells	61.9% of monocytes	Unclassified	Unclassified	monocyte
Glucose (mmol/L)	Unclear*	3.39	3.90	3.40	2.5~4.4
Synchronize blood glucose levels (mmol/L)	Unclear*	5.86	4.58	5.94	3.9~6.1
Chloride (mmol/L)	Unclear*	120	131	128	120~130
Synchronize blood chloride (mmol/L)	Unclear*	102	–	106	99~110
Microproteins (mg/dL)	Unclear*	107.5	51.8	35.9	15~45

Notes: *The lumbar puncture was performed in the patient 1 at a different hospital, some original data was untrackable.

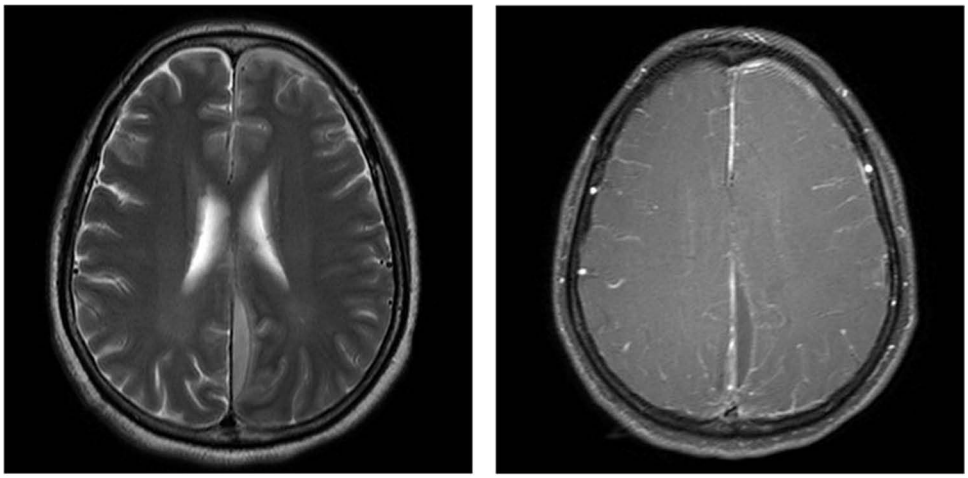

Figure 4 Cranial MR enhancement on July 28: There was meningeal thickening and abnormal enhancement, along with empyema adjacent to the cerebral falx and tentorium cerebelli. (**A**) T2 sequence showing a high signal bar on the left side of the cerebral falx, locally wrapped and considered to be empyema. (**B**) FLAIR sequence showing a low signal bar on the left side of the cerebral falx, locally wrapped.

limb movement, and were completely relieved after one month. Cranial MR findings from August 24th revealed a decrease in enhancement adjacent to the left cerebral falx and enhancement of the left tentorium cerebelli (Figure 6). Cranial MR findings on September 23rd demonstrated that the enhancement continued to decrease and that the cerebral edema had largely dissipated (Figure 7), the cerebrospinal fluid indexes improved. The cerebrospinal fluid and imaging findings are detailed in Table 2 and Figures 4–7.

Discussion

Bacterial meningoencephalitis is a group of common infectious diseases of the central nervous system characterized by fever, headache, impaired consciousness, seizures, and paralysis of the limbs. Rare symptoms include irritability or apathy as well as personality changes and behavior abnormalities.This disease is typically transmitted directly from the ear, sinus, mouth, and blood to distant sites such as the heart and lungs. A recent study revealed that odontogenic CAs frequently have unclear clinical features and an increasing incidence, and that patients diagnosed with diabetes are more likely to develop CA, indicating that maintaining oral health can help reduce the incidence of CA.[6] Multiple abscesses occur in 10% to 15% of CA cases, with a mortality rate ranging from 6% to 24%, and 30% to 56% of patients diagnosed with CA experience permanent neurologic complications.[7] With the advancement of medical technology, the incidence and disability of bacterial meningoencephalitis have significantly decreased. Nevertheless, the widespread use of antibiotics, universal vaccination, and the use of hormonal immunosuppressants have led to significant changes in the types of pathogenic bacteria of bacterial meningoencephalitis and their drug resistance. In addition to infections with common bacteria such as Streptococcus pneumoniae and Neisseria meningitidis, normal flora can also cause bacterial meningoencephalitis, with more severe and complex conditions and longer treatment duration.[8] It has been demonstrated that CAs have transitioned from a staphylococcal disease to *Staphylococcus intermedius* as the predominant pathogen. Prior to 1960, staphylococcus infections were the leading cause of CAs, accounting for over one-third of cases, while streptococcus infections accounted for approximately 30% of cases. However, in recent decades, the incidence of staphylococcus infections has decreased, while the prevalence of streptococcus infections has increased, with *S. intermedius* infections being primarily responsible for the formation of CAs.[9,10]

CAs caused by *S. intermedius* were first reported in 1975. In 2009, Masalma et al reported that around 25% of CA cases resulted from *S. intermedius* infections.[11] In 2012, a metagenome analysis of CAs exhibited that *S. intermedius* could be detected in the samples of 21.5% of patients with CA.[12] Multiple CAs are more likely to occur in patients with *S. intermedius* infections of the central nervous system, as reported by Hu et al.[13] Isern reported a case of multiple CAs

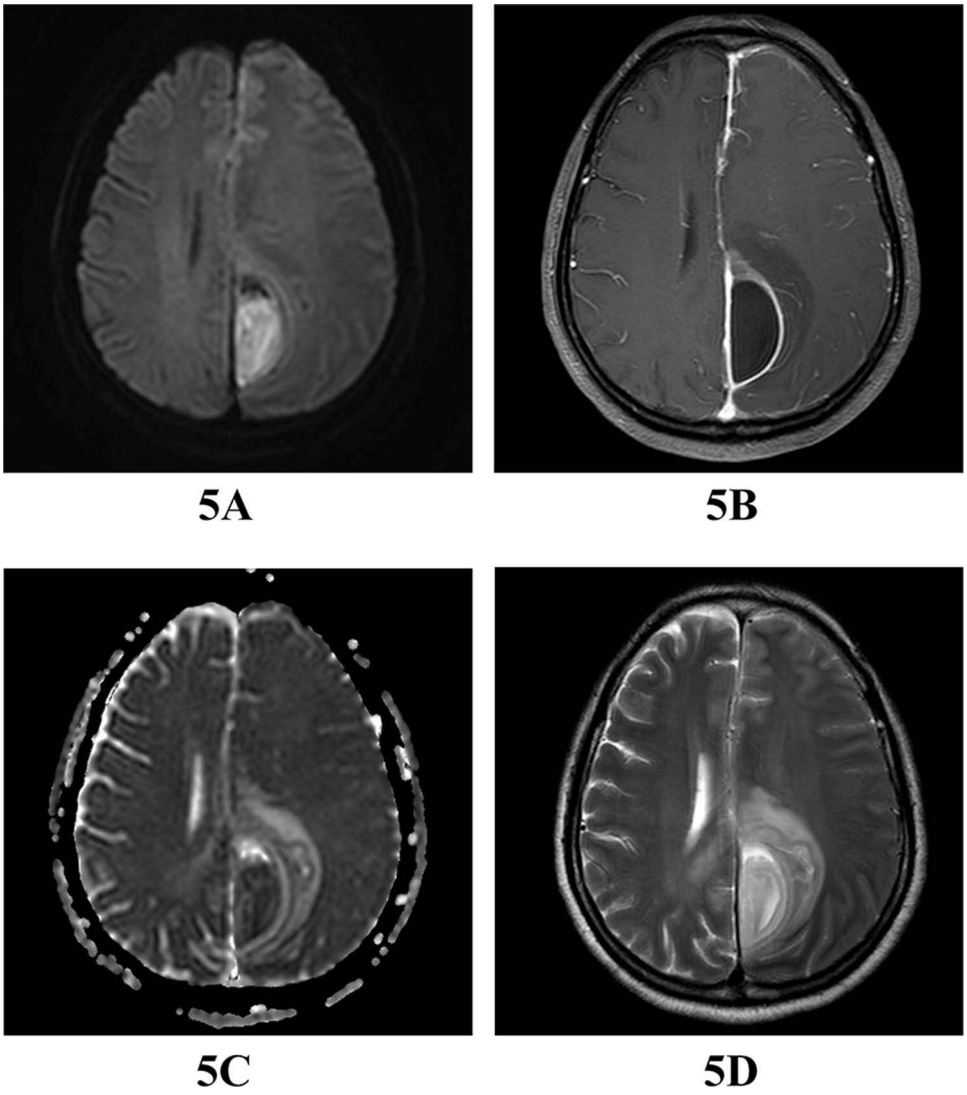

Figure 5 Cranial MR enhancement on August 13: Multiple abnormal signals were observed in the left frontoparietal lobe, the corpus callosum splenium, and the left temporal pole, along with thickening and abnormal enhancement of the meninges and empyema adjacent to the cerebral falx and tentorium cerebelli. (**A**) DWI sequence showing abnormally high signal in the left lateral semicircle of the cerebral falx, locally wrapped, with high signal on DWI. (**B**) Enhanced scan showing abnormally high signal in the left lateral semicircle of the cerebral falx, local encapsulation, local meningeal thickening, abnormal strengthening, and considered considered to be empyema. (**C**) ADC sequence showing abnormally high signal in the left side semicircle of the sickle, local encapsulation, hypoperfusion, and limited diffusion. (**D**) T2 sequence showing abnormally high signal in the left side semicircle of the falx of the brain, localized wrapping, and surrounding swelling.

with *S. intermedius* detected in the pus.[14] The study of Huashan Hospital showed that the pus wall thickness of single brain abscess caused by P. aeruginosa was thicker than that of other bacteria, and the edema was more obvious, but the difference in diameter of abscess was not statistically significant.[15] The case we studied was multiple brain abscesses with wide distribution and large number, consider that this may be an imaging feature associated with intermediate streptococcus, which may help in early diagnosis.

Meningoencephalitis caused by *S. intermedius* has complex clinical presentations, easily fluctuating conditions, and distinctive imaging characteristics; it is common in the elderly or in patients with underlying diseases and can be effectively treated by early diagnosis of the etiology and timely antibiotic adjustment. Kunapaisal reported a 13-year-old healthy adolescent with secondary CAs caused by decreased resistance after infection with SARS-CoV-2. Postoperative pathology showed positive PCR for intermediate streptococcus, and the patient had no neurological sequelae after treatment[16]. Fransson reported a 34-year-old man with apical periodontitis, endophthalmitis, and multiple CAs caused by *S. intermedius*, recommended doses of meropenem and vancomycin were used but the patient still ended up with the

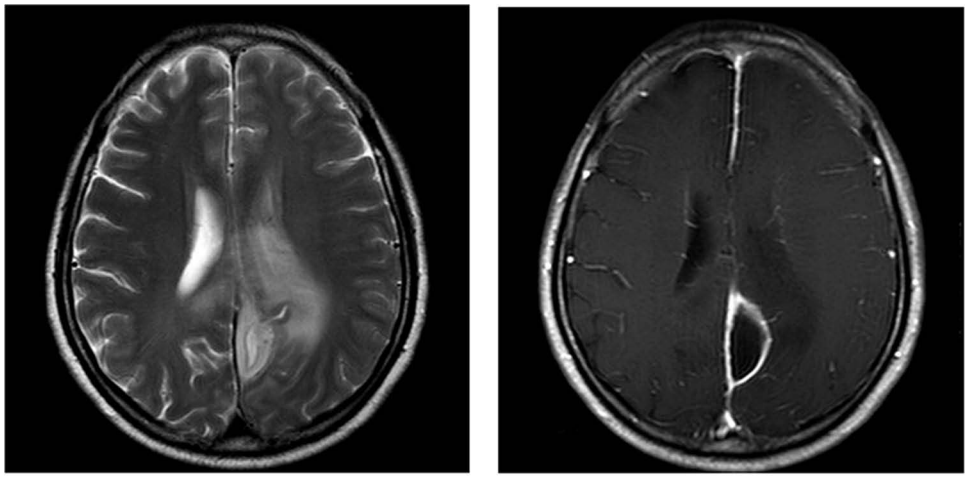

Figure 6 Cranial MR enhancement on August 24: Spindle-shaped ring enhancement was observed in the region adjacent to the left cerebral falx, the left tentorium cerebelli, and the adjacent brain parenchyma, where abnormal signals were still present. Compared to the previous MR, the range of enhancement and peripheral brain edema were reduced. (**A**) The T2 sequence shows a crescent-shaped high signal adjacent to the left side of the falx cerebri, with local encapsulation and surrounding edema. (**B**) T1 enhanced scan shows low signal intensity in the left hemisphere of the cerebral falx, local swelling, and ring-enhancement.

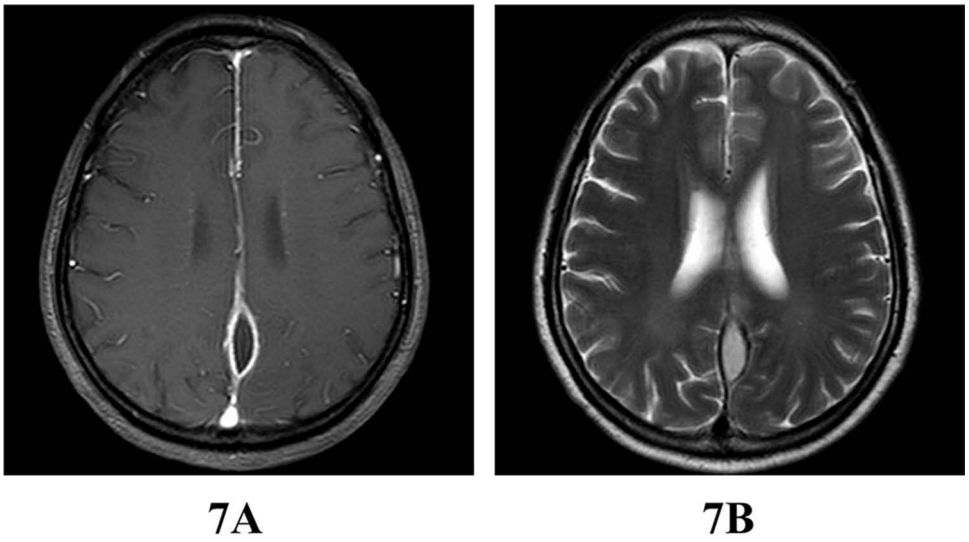

Figure 7 Cranial MR enhancement on September 23: Spindle-shaped ring enhancement was still visible in the region adjacent to the left cerebral falx and the left tentorium cerebelli, where abnormal signals were detected. In comparison to the previous MR, the extent of enhancement was diminished, and the original peripheral brain edema had dissipated. (**A**) The T1-enhanced scan shows spindle-shaped ring enhancement adjacent to the left side of the falx cerebri, with a reduction in size compared to the previous scan. (**B**) T2 sequence shows a high fusiform signal at the left side of the falx of the brain, which is smaller than before, and the primary peripheral cerebral edema is basically dissipated.

removal of the left eye, suggesting that kidney lesions can affect the drug's effect.[17] Previous research found that *S. intermedius* infections were present in the cerebrospinal fluid of a 67-year-old man who presented with coma and fever.[18] Meningoencephalitis caused by *S. intermedius* is relatively difficult to distinguish from tuberculous meningoencephalitis based on clinical manifestations and results of cerebrospinal fluid and MR imaging. Therefore, the diagnosis of this disease requires cerebrospinal fluid biochemistry, microscopic examination, culture, and PCR detection of bacterial DNA. The diagnosis is confirmed by relying on the bacterial culture of cerebrospinal fluids, and genome sequencing is beneficial for early and definitive diagnosis.[19] The systematic literature review by Brown revealed that even in resource-rich settings, the etiology of encephalitis can be determined in less than half of clinical cases. Next-generation sequencing

Table 2 Cerebrospinal Fluid Results of Patient 2

Time	June 28	August 6	October 11	Reference value
Pressure (mmH2O)	310	110	148	80~180
Leucocyte count (×10^6/L)	1022	350	8	0~5
Leucocyte percentage	88% of multinucleated cells	92% of monocytes	Not classified due to few leucocytes	Monocyte
Glucose (mmol/L)	2.65	1.84	2.64	2.5~4.4
Synchronize blood glucose levels (mmol/L)	6.5	6.5	4.98	3.9~6.1
Chloride (mmol/L)	118	112	119	120~130
Synchronize blood chloride (mmol/L)	95	92	100	99~110
Microproteins (mg/dL)	126.1	214.3	49.6	15~45

(NGS) is recommended as a first- or second-line test for the diagnosis of acute and chronic encephalitis based on growing evidence that it plays an important role in the detection of undiagnosed encephalitis.[20]

The 2017 Chinese expert consensus on the diagnosis and treatment of infectious patients in neurosurgical intensive care units recommends intravenous infusions of vancomycin combined with third- or fourth-generation cephalosporins or meropenem, along with linezolid in cases of resistance, insensitivity, and allergy to vancomycin.[21] In 2000, the British Society for Antimicrobial Chemotherapy recommended that antimicrobial treatment should last 4 to 6 weeks for patients with CAs undergoing surgical resection, 6 to 8 weeks for patients undergoing needle aspiration, and longer for patients receiving conservative treatment.[22] In our case, a combination of meropenem (2 g, intravenous [IV] injection every 8 hours) and linezolid (0.6 g, IV twice daily) with a synergistic effect were selected. Linezolid is a fully synthesized oxazolidinone antibacterial drug, which exerts antibacterial effect by inhibiting bacterial protein synthesis. Its site and mode of action are different from most antibacterial drugs, and it is not easy to cross drug resistance with other antibacterial drugs that inhibit bacterial protein synthesis, so the safety of clinical use is relatively high. The permeability is good, and the area ratio under the curve of cerebrospinal fluid concentration to serum concentration is close to 1.0, which is very beneficial for the treatment of central nervous system infection. Studies have shown that Streptococcus intermedia is sensitive to penicillin, ceftriaxone, levofloxacin, vancomycin, linezolid.[1,2] The first patients were administrated antibiotics for nearly 8 weeks, the second case for 7 weeks. Moreover, a previous study suggested that corticosteroids in conjunction with anti-infection treatment reduce the mortality of meningitis caused by *S. pneumoniae* and the incidence of severe hearing loss in children with meningitis caused by *Haemophilus influenzae*.[23] When the condition of the patients was at its most severe, we also administered a small dose of corticosteroids to reduce the inflammatory response for a brief period of time, Methylprednisolone 40mg 1 week, The first case used antibiotics for nearly 8 weeks, the second case for 7 weeks, and the patients' condition substantially improved after approximately four weeks of anti-infection treatment. After two years of follow-up, MRI revealed that the CAs gradually shrunk, and no recurrence occurred. The patient is conscious and has normal limb movement without convulsions, but the overall response is slow with hypomnesis. In these two cases, the imaging lesions were evident and multifocal, and a needle biopsy was not recommended due to the high surgical risk. Therefore, there was no gold standard pathologic result. Blood and cerebrospinal fluid cultures were negative. There was no dynamic review of imaging to finish normalizing cases, and the analysis of pathogenesis relied on high-throughput sequencing of cerebrospinal fluids, both of which contributed to a relative decrease in precision. Also, in the five years of clinical observation since 2018, only these two cases with imaging and NGS findings distinct from other infectious meningoencephalitis occurred. Ceftriaxone has a good ability to penetrate the central nervous system, but clinical observation on many central nervous system infection effect is not ideal, considering that it is related to the drug resistance of bacteria. This study has a small sample size, so the results may be biased. Clinical data will continue to be collected for long-term observation in the future.

Conclusion

In clinical work, for patients with acute onset of suppurative meningoencephalitis, if the condition improves at the beginning of treatment and the symptoms worsen later, brain MRI indicates multiple small abscesses, which should be suspected the infection with streptococcus intermedius, which need to be distinguished from tuberculous meningoencephalitis and brain malignancy. Further improvement of high-throughput sequencing of cerebrospinal fluid can assist in the definitive diagnosis. In this study, the combination of meropenem and linezolid for 4 to 6 weeks was recommended.

Data Sharing Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

This study was conducted with approval from the Ethics Committee of Zhongshan City People's Hospital. This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants to publish the case details.

Consent for Publication

All participants signed a document of informed consent.

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Disclosure

The authors declare that they have no competing interests in this work.

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