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CASE REPORT

The First Infant Anaerobic Meningitis Infected by *Prevotella bivia*: A Case Report and Literature Review

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Abstract: Anaerobic bacterial meningitis is a serious infection of the central nervous system (CNS) that leads to severe neurological complications, resulting in high levels of disability and mortality worldwide. However, accurately diagnosing and isolating the responsible pathogens remains challenging due to the difficulty in culturing anaerobic bacteria, as they require harsh anaerobic culture conditions. Anaerobic bacteria have rarely been reported in meningitis, especially in children. This report details the first infant with anaerobic meningitis caused by *Prevotella bivia*. Additionally, we present a case of infant anaerobic meningitis caused by *P. bivia*, detected using metagenomics next-generation sequencing (mNGS). Our clinical experience highlights the importance of early identification of *Prevotella* spp. through mNGS and anaerobic culture, the effectiveness of antimicrobial medications, and the timely implementation of carefully planned precision therapeutic regimens. Furthermore, we have conducted a comprehensive review of 10 cases of *Prevotella* spp. infection, summarized their clinical and laboratory examination characteristics, and identified their commonalities.

Keywords: *Prevotella bivia*, anaerobic meningitis, infant

Introduction

Prevotella spp., a diverse gram-negative obligate anaerobe, was first described in 1990 by Shar and Collins. It is the most heritable vaginal bacteria and is associated with increased body mass index.[1] The type species of *Prevotella melaninogenica* was initially described as *Bacteroides melaninogenica* in 1921, and *Prevotella bivia* was first described as *Bacteroides bivius* in 1977 by *Johnson* and *Holdeman*.[2] In addition, *Prevotella* spp. are also associated with human infections such as dental caries, as well as other conditions like intestinal diseases like ulcerative colitis.[1,3] *Prevotella* spp. have received less attention, possibly due to the challenges posed by its harsh anaerobic culture conditions. Meningitis caused by anaerobic bacteria is rare in both children[4] and adults,[5,6] which may explain why anaerobic meningitis caused by *Prevotella* spp. has been rarely reported worldwide. In this report, we present the first infant case of infant meningitis caused by *Prevotella bivia* isolated from cerebrospinal fluid. The patient has been improved and was successfully discharged following early laboratory identification and the timely implementation of carefully planned precision therapeutic regimens.

Case Report

An infant girl aged 2 months 21 days was brought to the emergency department of a children's hospital due to a continuous fever lasting 4 days; the infant's mother had a history of diabetes. At the beginning of the illness, her body temperature rose to 39°C but could be reduced to 38°C with physical cooling, accompanied by an elevated white blood cell count (WBC; 15.31 × 109/L) and C-reactive protein (CRP, 20.24mg/L). There was no apparent improvement in temperature after 4 days of treatment with ampicillin, ceftriaxone, hydrocortisone, dexamethasone, and Chinese patent medicine Xiaoer Chaigui Tuire granules. Additionally, symptoms of vomiting and upward gaze of the eyes appeared at 2 times.

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On 1 day of admission, the complete blood count revealed more elevated WBC (20.14 × 10^9 /L; neutrophils proportion=53.5%) and CRP level (35.19 mg/L, Table 1). The ultrasonography and enhanced MRI showed no obvious abnormal signal in the brain parenchyma (Figure 1A–D), with the presence of purulent and partial extracerebral fluid in the subarachnoid space. Cerebrospinal fluid (CSF) analysis indicated a severe bacterial infection (protein, 2960 mg/L; glucose, 0.05 mmol/L; WBC, 29.892×109 /L; neutrophil proportion=87%, Table 2). Thus, antibacterial therapy comprising meropenem (40 mg/kg, iv, q 8 h) and vancomycin (15 mg/kg, iv, q 8 h) was initiated, along with the use of dexamethasone (0.8 mg, iv, bid) to mitigate inflammation and adhesion. On day 3. Although no bacteria were cultured from the CSF in the 5% carbon dioxide culture, a very small number of gram-negative bacilli were observed under the microscope before cultured (Figure 1E). After four days of continuous treatment, the fever persisted. Following the second CSF analysis showing a slight decrease in intracranial infection markers (Table 2), meropenem and vancomycin were continued used for infection control, while administering mannitol for intracranial pressure reduction (20mL, iv, q8h).[6] On day 6, the ongoing rise in WBC in blood indicated no improvement in the infection, and piperacillin/tazobactam was added (0.74g, iv, q8h). Considering the persistent fever in the following two days, metronidazole targeting *P. bivia* was initiated (68 mg/kg, iv, q8h) on day 9. On day 11, the third CSF analysis indicated a significant improvement in intracranial infection. Over the next few days, the child's condition was stable, with no fever, and no convulsions. On day 16, the patient's complete blood count and CRP had returned to normal. The fourth lumbar puncture revealed clear CSF with a decreased neutrophil percentage, although protein and glucose levels had not yet normalized. The enhanced MRI indicated the presence of suppurative meningitis post-treatment, accompanied by bilateral subdural effusion and widened partial extracerebral fluid lacunae (Figure 1F–H). These demonstrate the efficacy of the anti-infective therapy. Therefore, the aforementioned anti-infective treatment regimen (meropenem + piperacillin / tazobactam + metronidazole) was continued for the next few days. On day 29, meropenem was replaced with chloramphenicol (17 mg, iv, q8h), and plasma was given as nutritional support (100mL, twice). The third entranced MRI showed that it consisted of suppurative meningitis after treatment, some extracerebral fluid lacunae widened, and there were a few short T2 signals in the left cerebellar sulci (Figure 1I–L).

On day 35, a granulocyte-stimulating factor was administered for neutropenia (0.42 × 10^9 /L). On day 37, due to the sixth CSF analysis showing no significant changes compared to the former, piperacillin/tazobactam was subsequently replaced with meropenem. Following a period of treatment, the child's general condition and weight improved. On the 40th day, enhanced MRI revealed partial absorption of intraventricular pus, and chloramphenicol was substituted with ampicillin (0.9g, iv, q8h), and immunoglobulin was initiated to support the treatment. On day 48, the child was discharged, and upon discharge, received metronidazole for two weeks (0.1g, po, q8h). On the 20th day post-discharge, the child's complete blood count and CRP were within normal ranges. Although the cerebrospinal fluid analysis has not fully recovered, the ultrasonography and enhanced MRI revealed a further reduction in bilateral subdural effusion (Figure 1M–1P). At the same time, the electrocardiogram is normal. Metronidazole has been taken orally since discharge. On the 62nd day post-discharge (Day 129), the child's CSF analysis had fully recovered, and the enhanced MRI revealed disappear in bilateral subdural effusion.

The Results of 2 Metagenomics Next-Generation Sequencing (mNGS) Examination of Cerebrospinal Fluid at Different Time

On day 3, the mixed bacterial sequences, including *P. bivia* (1521 reads), *P. disiens* (560 reads), *Streptococcus anginosus* (260 reads), *Peptostreptococcus anaerobius* (59 reads), *Bacteroides thetaiotaomicron* (36 reads) and *Bilophila*

Table 1 The Comparison Results of Blood Routine Examination at Different Times

Name	Day1	Day2	Day6	Day16	Day27	Day37	Day40	Day46	Day67
WBC count (×109 /L)	20.14	17.4	22.6	6.87	5.62	5.64	7.88	7.52	9.36
Neutrophils %	53.5	66.3	56.1	26.8	23.7	7.6	16.9	25.25	30.4
CRP (mg/L)	35.19	25.52	15.6	<0.499	<0.499	<0.499	<0.499	<0.499	3.34

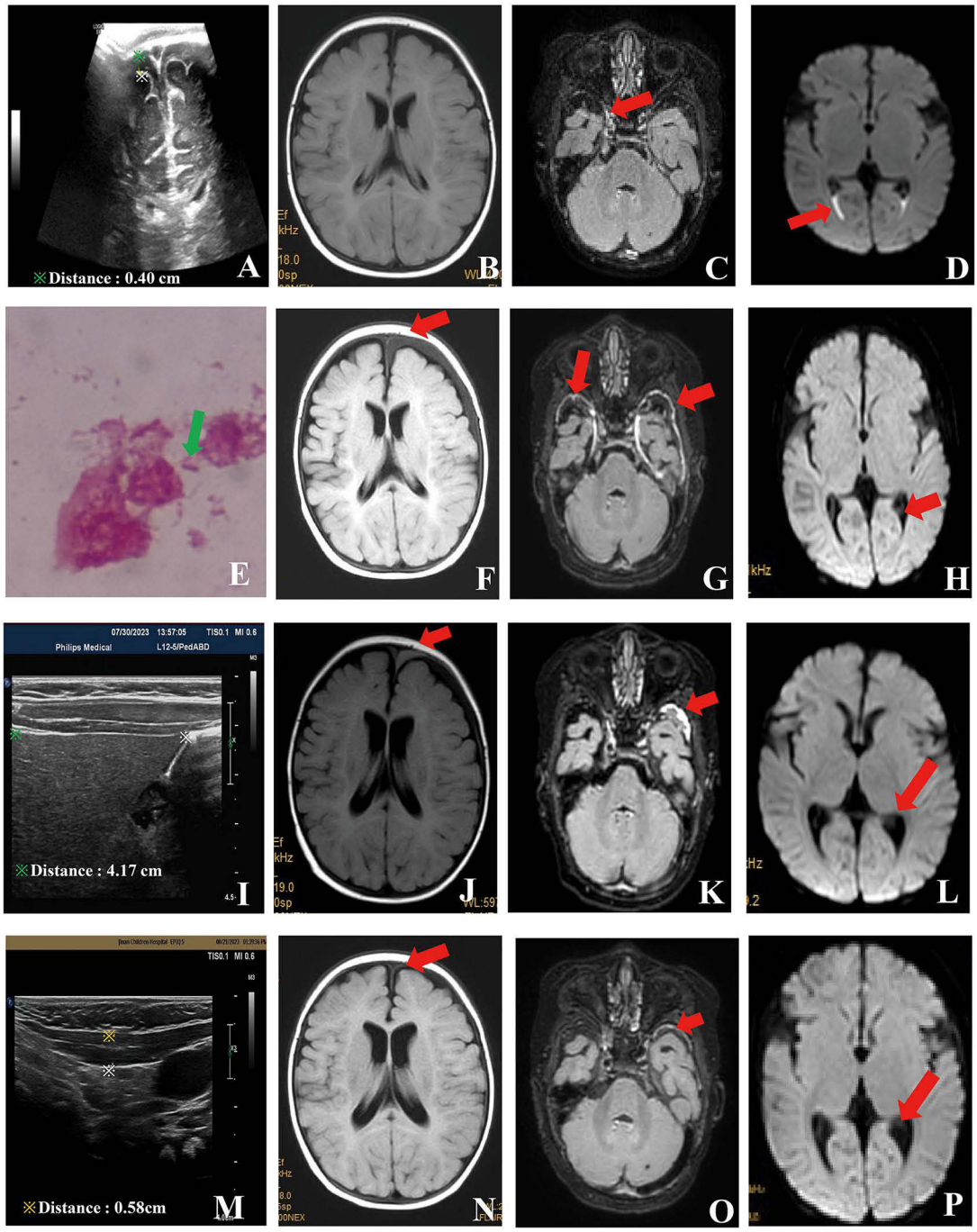

Figure 1 The laboratory, imaging, and pathology examination results related to the *Prevotella bivia* meningitis. The green arrow indicates the strain seen under the microscope of the CSF specimen, and the red arrows indicate the location of the imaging changes. (**A**) Ultrasonography revealed 0.4cm anechoic area in the subarachnoid space (Day 0). (**B**) T2-fluid attenuated inversion recovery (T2-FLAIR), no subdural effusion (Day 1). (**C**) T2-FLAIR revealed enhancement and linear hyperintensity in the right middle cranial fossa, indicating mild meningitis (Day 1). (**D**) Diffusion-weighted imaging (DWI) showed diffusion limitation of the posterior horn of bilateral ventricles, suggesting ependymitis and empyema (Day 1). (**E**) Microscope examination showed a small number of gram-negative bacilli (Day 1). (**F**) T2-FLAIR displayed slightly higher signal intensity in the lower stripe of the left frontal cranial plate (Day 13).(**G**) T2-FLAIR exhibited enhancement in the subdural effusion and linear high signal intensity in the bilateral middle cranial fossa, suggesting increased severity of meningitis compared to previous findings (Day 13). (**H**) DWI showed the disappearance of high signal in the posterior horn of bilateral ventricles, indicating the improvement of empyema (Day 13). (**I**) Liver volume increased by 4.17cm (Day 6). (**J**) T2-FLAIR revealed decreased subdural effusion in the left forehead and at the midline of the right subcostal clavicle (Day 31). (**K**) Enhanced T2-FLAIR indicated improved meningitis compared to the earlier result (Day 31). (**L**) DWI showed normal findings in the posterior horn of bilateral ventricles (Day 31). (**M**) Bilateral sternocleidomastoid muscle scan indicated a thickness of approximately 0.60cm for the right muscle and 0.58cm for the left muscle (Day 27). (**N**) T2-FLAIR demonstrated significantly reduced left subdural effusion compared to the previous result, indicating basic absorption (Day 31), with further improvement on Day 69. (**O**) Enhanced T2-FLAIR indicated improved meningitis (Day 69). (**P**) No abnormalities were observed in the posterior horn of bilateral ventricles (Day 69).

Table 2 The Comparison CSF Results of Lumbar Puncture at Different Times

Name	Day 1	Day 4	Day 11	Day 16	Day27	Day37	Day40	Day46	Day67	Day 129
Character	Off-White and Cloudy	Off-White and Cloudy	Light Yellow and Faintly Cloudy	Colorless	Colorless	Colorless	Colorless	Colorless	Colorless	Colorless
Glucose (mmol/L)	0.05	0.19	0.84	1.2	1.21	1.4	1.5	1.21	1.83	2.47
Protein (mg/L)	2960	2253	2504	713	844	817	992	877	547	351
Chlorion (mmol/L)	117	125	118	123	125	123	124	125	124	121
WBC count (×109 /L)	29.892	22.024	0.412	0.156	0.209	0.311	0.359	0.350	0.155	0.025
Neutrophils %	87	70	70	20	14.3	28.6	25	20	18	8
Mononuclear cells %	13	30	30	80	85.7	71.4	75	80	82	92

wadsworthia (26 reads) (Figure 2A), were detected using mNGS (Weiyuan Gene Technology Co., LTD, Nanjing, China) from the cerebrospinal fluid, the coverage of sequencing *P. bivia* is 2.1360% (Figure 2B). On day 11, the second NGS examination of cerebrospinal fluid showed that trace amounts of anaerobic and aerobic bacterial sequences were still detected, the reads of *P. bivia* are down to 42 (Figure 2C).

Discussion

Bacterial meningitis ranks among the top ten causes of infection-related deaths worldwide,[7] and continues to pose a significant global health challenge for both children and adults in the post-COVID-19 era. While anaerobic meningitis is very rare, it represents a severe CNS infection associated with high disability and mortality.[4–6] Anaerobic meningitis has been reported to account for only 2.4% of bacterial meningitis, significantly below its true clinical proportion due to the challenges of culturing under harsh anaerobic conditions.[6] In our review, we conducted s search on PubMed for all the published cases of co-infection anaerobic meningitis caused by *Prevotella* spp. and *Bacteroides* spp. in the English literature.[1,2] We collected 10 cases (excluding our patient) in the 10 published articles (Table 3).[8–17] Among these 10 cases, there were 3 females and 7 males, with a female/ male ratio of 3:7, and the mean age of people was 31.4 (ranging

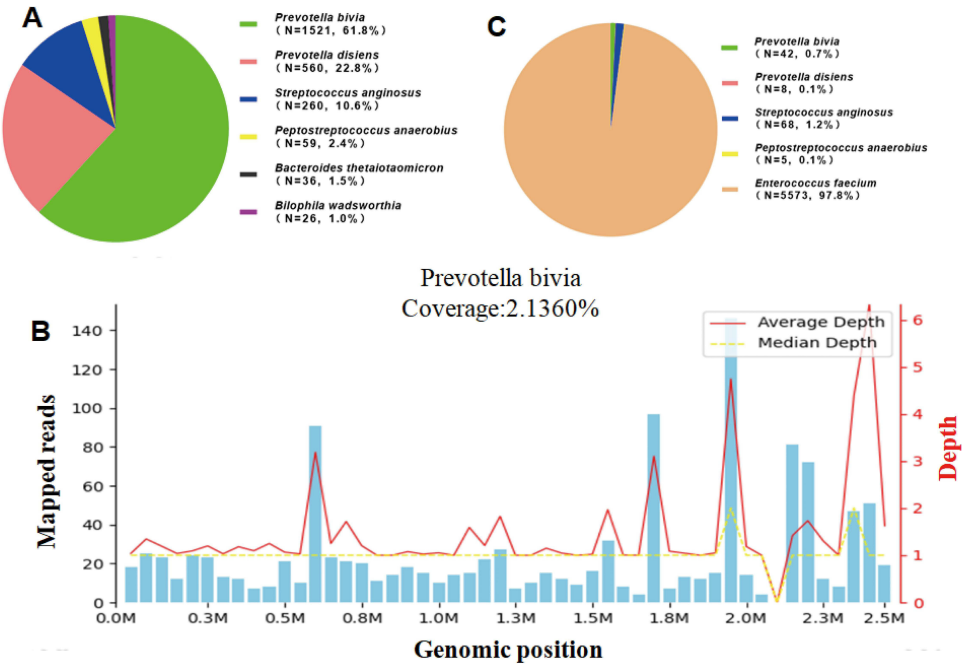

Figure 2 The anaerobic bacteria detected by mNGS. (**A**) The anaerobic bacteria found in the CSF during the initial mNGS analysis. *P. bivia*: 1521 reads; *P. disiens*: 560 reads; *S. anginosus*: 260 reads; *P. anaerobius*: 59 reads; *B. thetaiotaomicron*: 36reads; *B. wadsworthia*: 25reads; (**B**) The anaerobic bacteria identified in the CSF during the subsequent mNGS analysis. *Enterococcus faecium*: 5573reads; *Streptococcus anginosus*: 68reads; *P. bivia*: 42reads; *P. disiens*: 8 reads; *P. anaerobius*: 5 reads; (**C**) The mapped results and genomic position detected by mNGS.

Table 3 Reported Cases of Anaerobic Meningitis Infected by Prevotella sp

Author	Bacteria	Methods of Identification	Treatment	Treatment Times	Type of Pathogeny	Outcome	Reported Year	Sex/ Age (Years)
Chattopadhyay B. et al[8]	*Bacteroides fragilis*	CSF culture	Metronidazole	Unreported	Long-standing history of chronic otitis media	Recovery	1977	M/83
Odugbemi T et al[9]	*Bacteroides fragilis*	CSF culture	Metronidazole, clindamycin, cefoxitin	2 days	Chronic otitis media	Death	1985	M/6
N Busch et al[10]	*Fusobacterium necrophorum*. *P. bivia*	Blood and CSF cultures	Metronidazole	Metronidazole 5 weeks,	Tonsillitis sepsis with meningitis and mononucleosis	Recovery	1996	M/18
Itzhak Brook[11]	*P. intermedia*	CSF culture	Ceftriaxone and metronidazole	Metronidazole and ceftriaxone 21 days, Metronidazole 21 days	Meningitis associated with cerebrospinal fluid	Recovery	2003	M/16
Manoj K. Mittal et al[12]	*Staphylococcus aureus*, alpha hemolytic *Streptococci*, and *Eikenella* species; and *Prevotella intermedia, Fusobacterium* species, and *P.anaerobius*	CSF culture	Ceftriaxone and metronidazole	3 weeks	Pansinusitis with meningitis and epidural abscess.	Recovery	2009	F/11
Senthilkumar Sankararaman et al[13]	*Prevotella* spp.	Peritonsillar pus culture	Vancomycin, ceftriaxone, and metronidazole	6 weeks	Brain abscess	Recovery	2012	F/9
Xiaoqiang Li et al[14]	*Porphyromonas gingivalis, P. enoeca* and *Actinomyces israelii*	mNGS of cerebrospinal fluid	Ceftriaxone, vancomycin, and metronidazole	1 month	Brain swelling and the skull base was eroded	Recovery	2020	F/16
Vyshak Chandra et al[15]	*Streptococcus constellatus, Fusobacterium* species *P. dentalis*, and *Parvimonas micra*	Culture of the tumor	Vancomycin, ceftriaxone, and metronidazole	6 weeks	Right hemiparesis and meningioma	Recovery	2020	M/70
Wei-Wei Zhang et al[16]	*P. oris*	mNGS of cerebrospinal fluid	Metronidazole and meropenem	Metronidazole and meropenem 2 weeks, meropenem 2 weeks	Meningitis and spinal canal infection	Recovery	2023	M/9
Eric Heintz et al[17]	*Porphyromonas endodontalis, F.nucleatum, S. constellatus, Prevotella* spp.and *Parvimonas micra*	mNGS of cerebrospinal fluid	Cefepime and metronidazole, ceftriaxone and metronidazole	Cefepime and metronidazole 3weeks, ceftriaxone and metronidazole 3 weeks	Hydrocephalus.	Recovery	2023	M/40

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from 6 to 83 years). Among the reported 10 cases, the pathogens obtained by traditional culture were 7 cases, while the remaining 3 cases were obtained by mNGS. Notably, 3 out of the 4 cases reported between 2020 and 2023 were detected by mNGS. mNGS, an emerging and promising diagnostic tool, can identify more than 20,000 kinds of potential causes (bacterial, viral, fungal, tuberculosis, parasitic, and so on), thereby improving the clinical ability to identify novel or unexpected pathogens, such as COVID-19.[18] It also offers the advantages of being unaffected by antibiotic use, low cost, and rapid turnaround time.[19]

Upon diagnosis of *Prevotella* spp. infection, all patients were treated with metronidazole. Among the 10 reported cases, 9 cases were recovery, and 1 succumbed to the infection. There are several antimicrobial agents which are susceptible to *Prevotella* spp. that can penetrate the blood-brain barrier, including chloramphenicol, meropenem, and others,[20] the concentrations of chloramphenicol can reach 40–70% of serum levels in the CSF,[21] owing to its lipid solubility that aids in crossing lipid barriers and achieving high CNS concentrations. However, its use is limited in patients with fatal aplastic anemia and dose-dependent leukopenia.[20] In our case, the use of chloramphenicol resulted in a decrease in WBC, leading us to switch to meropenem. Both metronidazole and carbapenems can achieve high concentrations in the CSF.[21] When facing a mixed infection, where metronidazole is ineffective against aerobic bacteria and some gram-positive anaerobic bacteria, antimicrobial agents that are effective against these potential pathogens, such as ceftriaxone, which penetrates well into the cerebrospinal fluid and was administered simultaneously to our patients to obtain such coverage, should be combined to use.[11] Among the 10 reported cases, 5 involved mixed infections treated successfully with metronidazole, ceftriaxone (or cefepime), and vancomycin, and they were finally cured. The duration of antimicrobial therapy depends on the patient's response and underlying disease, typically lasting at least 2 weeks, but the final length must be adjusted based to the clinical situation,[21] the treatment cycles ranged from 3 weeks to 6 weeks in the 9 cured cases. In our successfully treated infant cases, we used metronidazole for 42 days, meropenem for 41 days, and chloramphenicol for 12 days.

Due to the lack of experience in the treatment of *P. bivia* encephalitis and the infant's condition recurred, a total of nine lumbar punctures were performed every two weeks, under the informed consent of the parents, to monitor the infant's treatment progress and adjust antibacterial drugs accordingly. Generally, the glucose level showed an upward trend, while protein and WBC exhibited a downward trend. Additionally, the proportion of neutrophils in WBC gradually decreased in the course of treatment. After a period of treatment, the child's general condition stabilized, body temperature normalized, and inflammation indicators returned to normal. Simultaneously, enhanced MRI revealed the absorption of intraventricular pus. These results collectively suggest that the efficacy and success of the treatment. Unlike traditional bacterial encephalitis, the successful treatment experience in this case indicates that clinical treatment may not necessarily depend on the return of WBC count in the cerebrospinal fluid to normal. This observation may be related to the immature blood-brain barrier in infants or damage caused by anaerobic bacteria.[7] As Shilo et al reported, several bacteria, including *P. copri*, with significantly higher scores in diabetes patients might be associated with diabetes affecting the gut and vaginal microbiome.[22] The infant's mother has gestational diabetes during pregnancy, and the presence of *P. bivia* in the infant's cerebrospinal fluid may be linked to the mother's hyperglycemia.

Conclusions

In conclusion, we have reported the first case of infant anaerobic meningitis caused by *P. bivia*. Throughout the treatment process, precise microbiological diagnosis, imaging support, interdisciplinary collaboration, and the effective utilization of mNGS technology were crucial for the successful management of anaerobic meningitis in infant caused by *P. bivia*. In addition to other advancements, particularly in conventional culture methods that are not effectively culture disease-causing pathogens, mNGS technology has significant potential to improve the clinical applications.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Statement

This study was approved by the Ethical Review Committee of Children's Hospital Affiliated to Shandong University (approval no. SDFE-IRB/P-2022017).

Consent to Publish

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication without any potentially identifiable images or data included in this article.

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Disclosure

The authors declare no competing interest in this work.

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