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CASE REPORT

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Brain abscess caused by *Streptococcus pyogenes* with atypical symptoms: a case report and literature review

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Abstract

Background *Streptococcus pyogenes* is a common gram-positive bacterium, belonging to group A *Streptococcus* (GAS), and is responsible for causing a range of clinical conditions. Brain abscess caused by GAS is uncommon in pediatric infectious diseases, and GAS brain abscess without acute infectious symptoms has been rarely reported.

Case presentation We present a case of one GAS brain abscess in a previously healthy child with unusual clinical manifestations of decreased muscle strength in the left limbs. The right frontal lobe mass lesion was resected using a microscope-based neuronavigation system. A sole defectively beta-hemolytic *Streptococcus pyogenes* was isolated from the lesion. The patient's peripheral blood whole-exome and the pathogen's whole-genome sequencing were performed respectively, revealing a heterozygous mutation in the interferon regulatory factor-8 (*IRF8*) gene in the patient and lack of hyaluronic acid capsules in *Streptococcus pyogenes* (genotype *emm*22). The patient eventually recovered after prompt surgical drainage of the abscess and appropriate antibiotic treatment.

Conclusions It is important to pay attention to *Streptococcus pyogenes* brain abscesses with mild clinical manifestations. Upon reviewing all the cases of pediatric GAS brain abscess reported in the published literature, we discovered that early diagnosis and treatment are crucial factors that impact the prognosis of GAS brain abscess.

Keywords *Streptococcus pyogenes*, Brain abscess, Child

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Background

Streptococcus pyogenes, a member of the group A *Streptococcus* (GAS) family, is a common pathogen causing skin and soft tissue infection, suppurative pharyngitis, tonsillitis, and scarlatina [1]. Recent reports of the re-emergence of invasive GAS infections have exacerbated public health concerns [2]. GAS has rarely been reported as a cause of brain abscess, a life-threatening infection in children [3, 4]. The clinical symptoms of GAS brain abscess are usually severe, such as high fever, severe headache, and projectile vomiting [5–13]. However, we here report a rare case of GAS brain abscess caused by *Streptococcus pyogenes* in which the initial symptom was only mild decreased muscle strength in the left limbs. Additionally, we summarize the 13 pediatric GAS brain abscess cases from the literature.

Case presentation

A previously healthy 2-year-old girl was admitted to our hospital with a primary complaint of decreased muscle strength in the left limbs for three days. She did not report any fever, rashes, headache, vomiting, sore throat, or cough. Her temperature, respiratory rate, heart rate, and blood pressure were all within normal range. Two weeks before admission, her parents squeezed a skin abscess (about 1-centimeter-diameter) on her left leg, which healed soon. She had no history of suppurative tonsillitis, pharyngitis, otitis media, mastoiditis, or sinusitis, and had never undergone bacterial culture testing. The parents denied any history of streptococcal infection, medical issues, or psychosocial problems within the family.

Her physical examinations on admission were normal, but a Medical Research Council grade 4 weakness could be detected in her left limbs. Brain-enhanced magnetic resonance imaging (MRI) showed a right frontal lobe mass lesion, which was suggestive of a high-grade glioma or cerebral abscess (Fig. 1, a1–4). The abdominal B-ultrasonic examination, electroencephalography, and chest computed tomography scan showed no abnormality.

On the third hospital day, the patient suffered convulsions in the left leg for 3–4 min. A lumbar puncture was carried out, and the cerebrospinal fluid (CSF)showed normal levels of cells, glucose, and protein. The CSF culture was negative. Additionally, the blood cultures also yielded negative results. The patient received the sodium valproate injection (32 mg/kg) for four days. Two days later, the patient developed a fever, and on the next day, deep supratentorial lesions were resected using a microscope-based neuronavigation system. Intraoperatively, a localized, soft, and fish-like lesion was found at the top of the frontal lobe (Fig. 2). A thick abscess wall was observed after draining 10 mL of thick pus. A drainage tube was placed in the cavity formed after the excision of

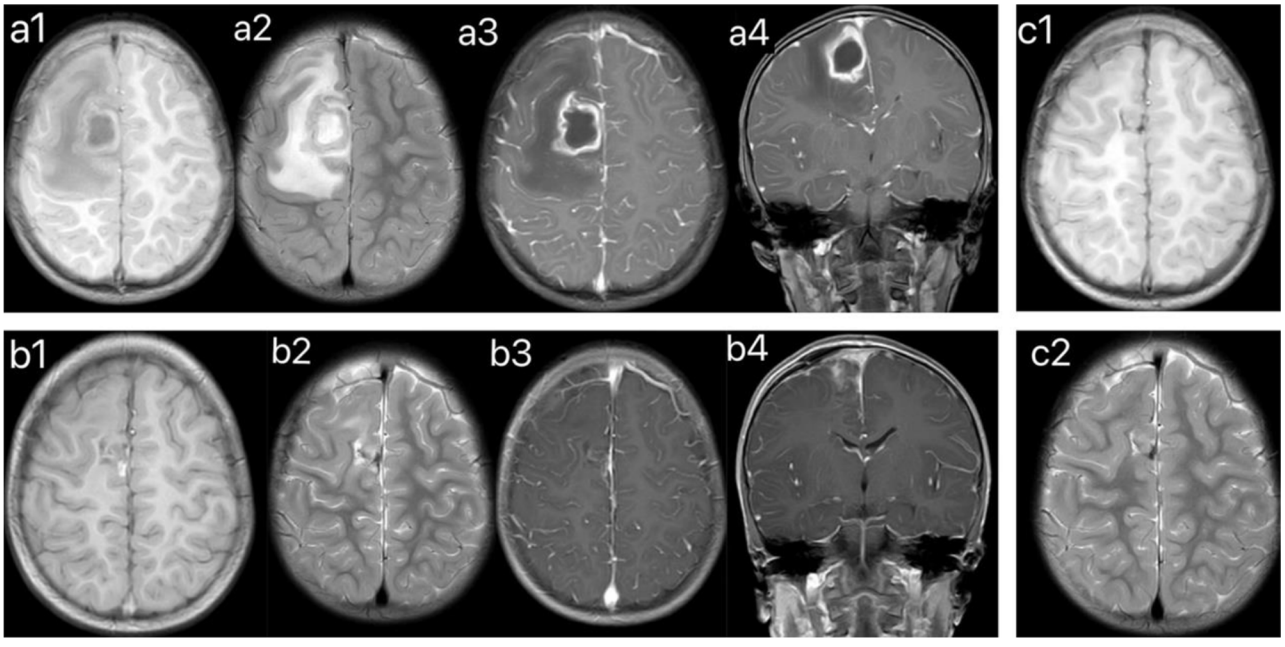

Fig. 1 Brain MRI images of the patient. *Note* **a1**–**4**, scanned before the operation. The axial T1-weighted image (**a1**) and T2-weighted image (**a2**) show the right frontal lobe had a large cavity which is a low signal in the T1 and a high signal in the T2; the axial (**a3**) and coronal T1-weighted contrast enhancement images (**a4**) show the ringwise enhanced lesion and peripheral edema without contrast enhancement. **b1**–**4**, scanned on the 19th day after the operation. The axial T1-weighted image (**b1**) and T2-weighted image (b2) show the lesion absorbed and narrowed considerably; the axial and coronal T1-weighted contrast enhancement images (**b3**, **b4**) show the ringwise enhanced lesion shrank obviously. c1 and c2, scanned 3 months after the operation. The axial T1-weighted image (**c1**) and T2-weighted image (**c2**) show the lesion was cured essentially

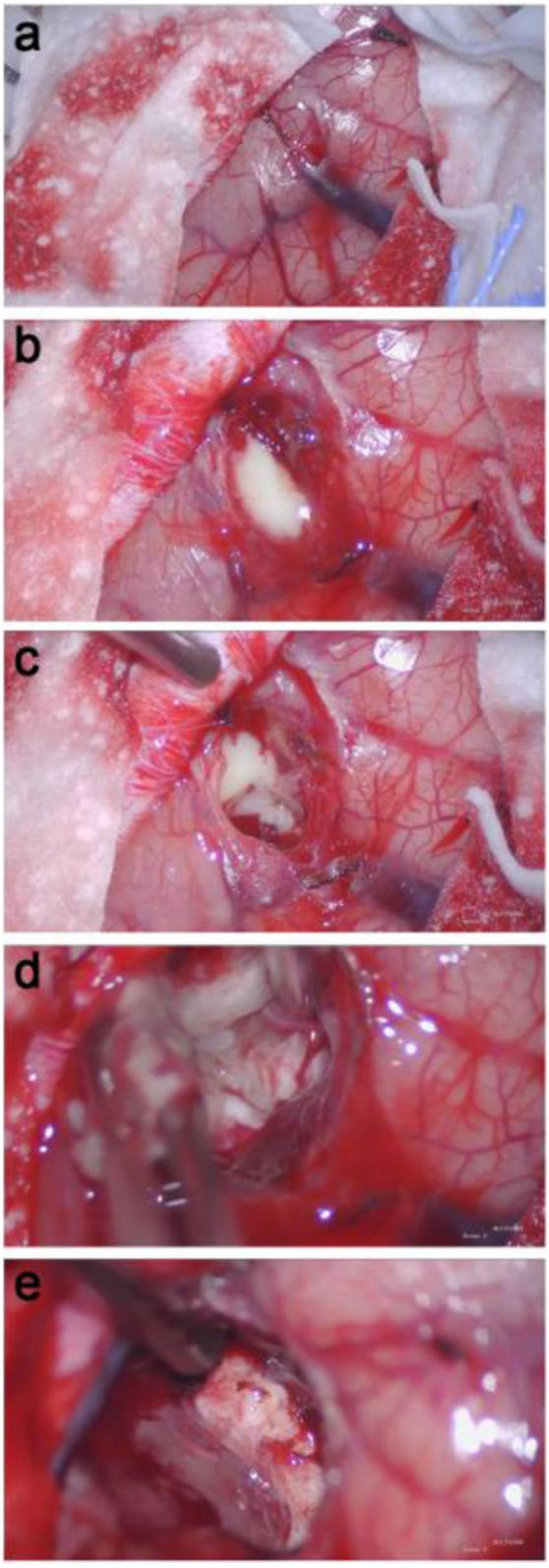

Fig. 2 Preoperative and postoperative visual fields. *Note* **a**, the frontal lobe mass lesion; **b** and **c**, thick pus in the abscess; **d**, thick abscess wall was found after pus was drawn off; **e**, abscess wall was moved

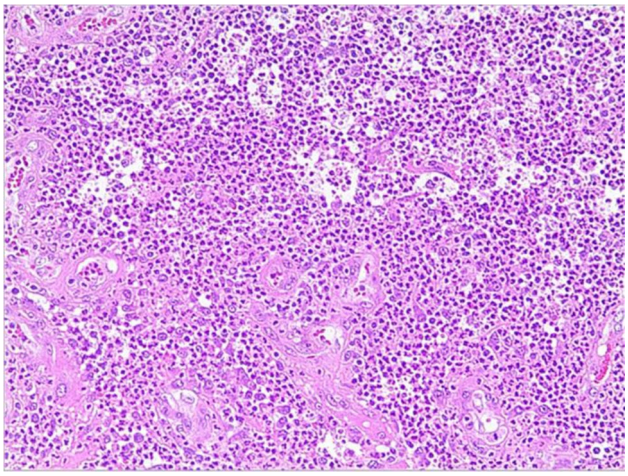

Fig. 3 Hematoxylin and eosin stain of the partially liquefied brain tissue (×200)

the abscess wall. In the process of operation, cefuroxime (50 mg/kg) was used via intravenous drip.

The abscess material was aspirated and then transferred to the clinical laboratory for aerobic and anaerobic culture. A sole defectively-beta-hemolytic *Streptococcus pyogenes* was isolated, which was identified by using both the VITEK COMPACT system (Mérieux, France) and matrix-assisted laser desorption ionization time-of-flight mass spectrometry (Bruker, Germany), and further identification was performed by 16 S rRNA analysis. No anaerobes were identified. The antimicrobial susceptibility test was performed by using the Kirby-Bauer method according to the criteria of the Clinical and Laboratory Standards Institute (M100-ED31). Antibiotics susceptibility test showed that it was sensitive to penicillin, ceftriaxone, vancomycin, and linezolid, but resistant to erythromycin and sulfamethoxazole. The histopathological findings of the removed tissue revealed partially liquefied brain tissue with collections of neutrophils and numerous pus cells (Fig. 3).

After surgery, the patient was promptly given empirical antibiotic therapy with vancomycin (20 mg/kg, q8h, 20 days) and meropenem (40 mg/kg, 12 days), and also took oral levetiracetam (10 mg/kg, 12 days). Seven days later, the abscess cavity drainage tube was removed. The patient's condition improved postoperatively, with decreasing white blood cell (WBC) counts, neutrophil counts, and C-reactive protein (CRP) levels (Fig. 4). MRIs 19 days after the operation showed almost complete resolution of the abscess (Fig. 1, bFigs. 1, 2, 3 and 4). Starting from the 26th day, the patient began oral linezolid treatment (5 days in the hospital and 7 days after discharge). On the last hospital day (29th day), the anti-hemolysin O antibody was measured at 8.8 IU/mL, and the levels of immunoglobulin A, G, and E were normal, so the patient was discharged. Three months later, follow-up MRIs

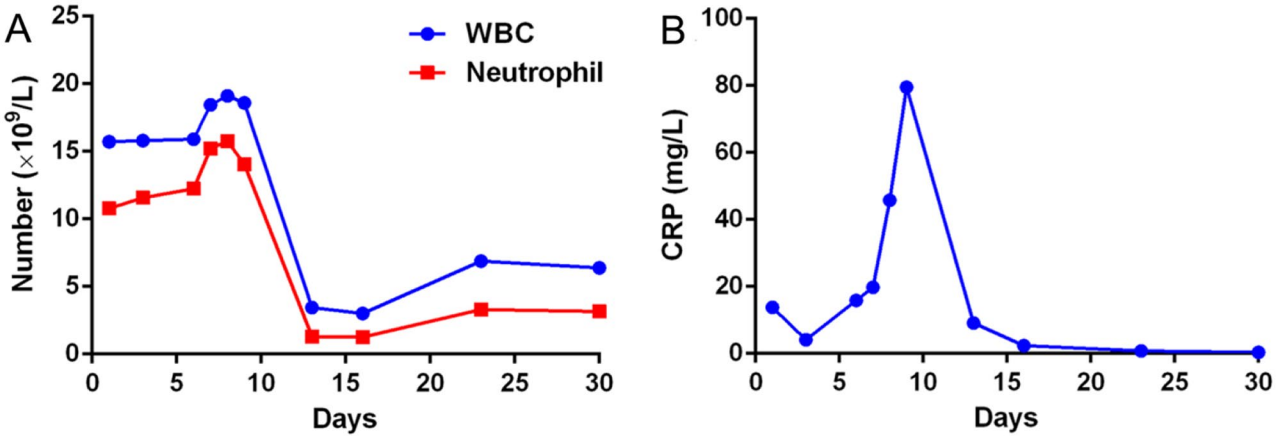

Fig. 4 Changing of WBC counts, neutrophil counts, and CRP levels over time. **A** WBC counts and neutrophil counts in peripheral blood. **B** CRP levels in peripheral blood during the course of the illness

showed complete recovery (Fig. 1, cFigs. 1 and 2). After 6 months of follow-up, the patient had no seizures and no obvious neurological sequelae.

Since some rare genetic diseases such as dystonia and seizures may show similar clinical manifestations with central nervous system infections, the possibility of the patient's congenital immune deficiency should be excluded. During the hospitalization, whole-exome sequencing was performed by MyGenostics Inc. (Beijing, China) based on the patient and her parents' peripheral blood samples. No immunodeficiency disease was identified, except a C497T (Pro166Leu) heterozygous mutation in the *IRF8*, inherited from the patient's mother (Fig. 5).

At the same time, the whole-genome sequencing of the isolated *Streptococcus pyogenes* was performed by Majorbio Bio-Pharm Technology Co. Ltd. (Shanghai, China). The complete genome sequence has been deposited in NCBI GenBank under accession number PRJNA835576 (BioProject) and Chromosome CP097251 (GenBank). Genetic analysis based on the Centers for Disease Control and Prevention Streptococcus laboratory database revealed that this isolation belonged to the genotype *emm22* and sequence type 46 (ST46).

Discussion and conclusions

Brain abscess caused by *Streptococcus pyogenes* belongs to a rare invasive infectious disease and might be associated with adjacent infection lesions, such as otitis media, mastoiditis, and sinusitis [3, 4]. Based on the literature published since 1988, only 13 pediatric cases have been reported (Table 1) [6–14]. Clinical manifestations in patients with invasive GAS infection were usually acute and severe, such as high fever, chills, weakness, and mental fatigue. Except for one case (NM) and the one we presented here, all the other reported cases (11/11, 100%) had acute severe clinical presentations, including fever ($n=8$), vomiting ($n=7$), lethargy ($n=6$), headache ($n=2$) and nuchal rigidity ($n=2$) [6–13]. In this case, the patient's clinical manifestations were mild, only decreased muscle strength. The patient did not have otitis media complication, however, she had a history of pre-infection as a skin abscess in the left leg two weeks ago. In our previous studies about the invasive *Streptococcus pyogenes* disease, 31.8% of the patients had skin or soft tissue infections as predisposing factors [5]. We speculated that the skin abscess might be caused by the GAS infection, and the bacterium might invade the bloodstream in the process of extrusion, break through the blood-brain barrier, and form a brain abscess. The abscess wall in the brain was thick, which was consistent with the long course of the disease. Although GAS brain abscesses are life-threatening infections, a satisfactory recovery (83.33%, 10/12) could be found with early diagnosis and appropriate treatment [6–8, 12–14]. In our previous study, *Streptococcus pyogenes* showed sensitivity to penicillin, ceftriaxone, cefotaxime, vancomycin, and linezolid [5]. Similar to the reported GAS brain abscess antibiotic treatment (Table 1) [7–9, 12–14], in this case, cefuroxime was administered via an intravenous drip during surgery, and empirical antibiotic therapy with vancomycin and meropenem was performed after surgery. After the pathogen was identified as GAS, meropenem was not promptly discontinued, and vancomycin was replaced by oral linezolid for 12 days after 20 days of treatment. The overall antibiotic treatment lasted 32 days. The assessment of antibiotic susceptibility in *Streptococcus pyogenes* isolates is essential for the formulation of efficacious therapeutic strategies. In this case, our findings indicate that *Streptococcus pyogenes* exhibits susceptibility to penicillin, ceftriaxone, vancomycin, and linezolid while resisting erythromycin and sulfamethoxazole. Given the rarity of penicillin-nonsusceptible strains, penicillin G remains the antibiotic of choice for treating infections attributable to *Streptococcus pyogenes*.

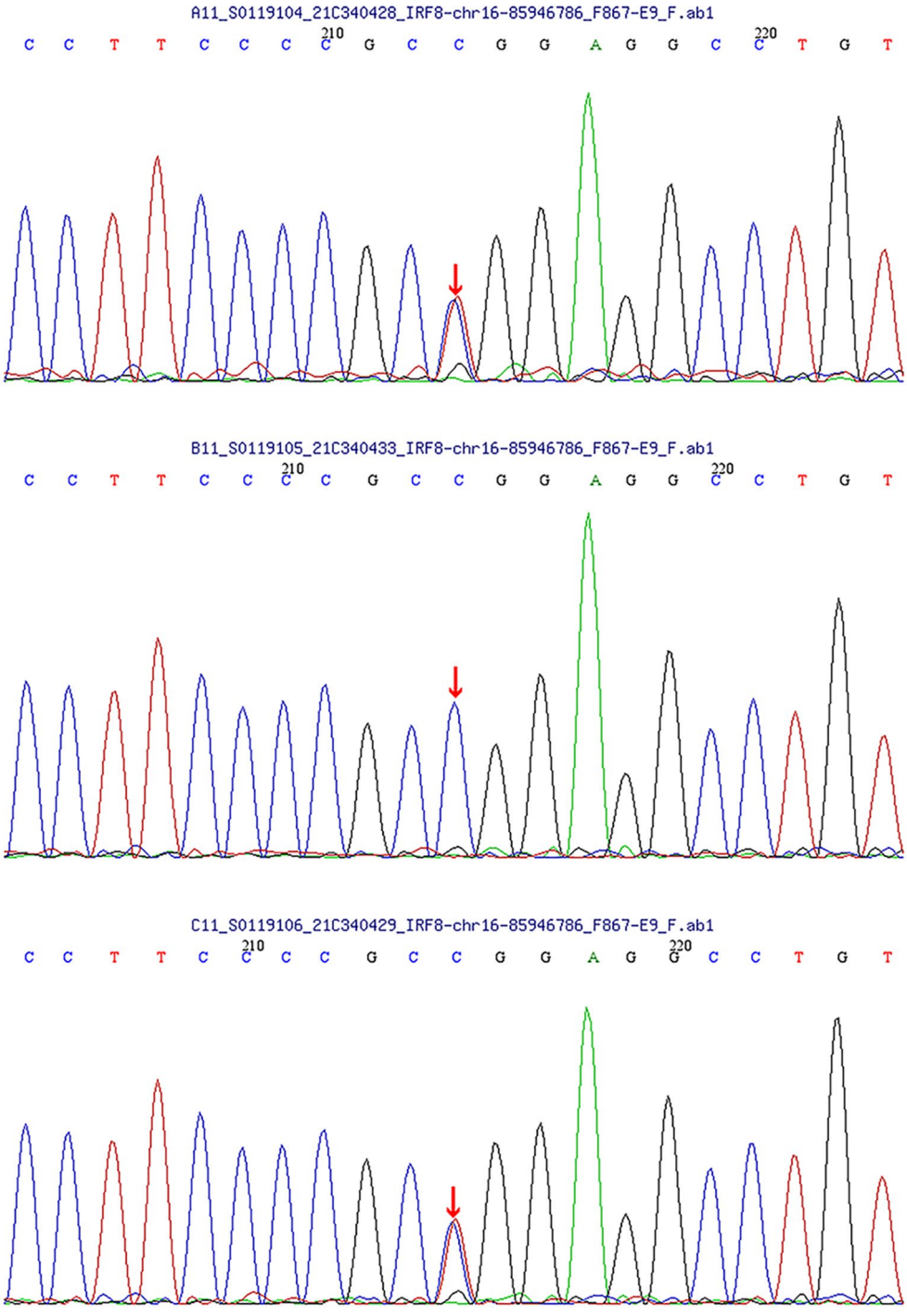

Fig. 5 Sequences including a C497T heterozygous mutation in *IRF8* gene. *Note* The arrowed locus was the 497 bp mutation locus in the IRF8 gene from the patient (up), her father (middle), and mother (down), and C497T base mutation causing Pro166Leu mutation in the production of the IRF8 gene

Macrolides have been conventionally employed as alternative therapeutic agents when patients exhibit penicillin allergy. However, our preceding research revealed a concerning prevalence of resistance, with 88.9% of clinical isolates exhibiting resistance to erythromycin and 81.4% to clindamycin, suggesting that macrolides may not constitute viable alternatives in China [5]. For the management of brain abscesses induced by *Streptococcus pyogenes*, a combinatorial regimen of penicillin G with either vancomycin or linezolid is advocated as the optimal treatment protocol. The standard duration for antibiotic therapy spans 4 to 6 weeks. In the event of penicillin

Table 1 Overview of pediatric case reports on GAS brain abscess

Age(y) and gender	Predisposing condition, signs, and symptoms	Abscess location	Emm/T type	Surgical treatment	Antibiotics (duration of therapies)	Outcome	Ref.
12, F	NM	Parietal	Emm1/T1	Aspiration	CXM + PCG (13 d) + CAP (4 w)	Recovery	[14]
10, M	Headache, vomiting	Temporal	NM	Craniotomy	PCG (10 d) + MNZ (10 d) + AMX (3 w)	Recovery	[6]
1.5, M	Acute otitis media, vomiting, lethargy, convulsions	Parietal, Temporal	Emm12/T12	Drainage	MEPM + VCM (2 d) + PCG + CTRX (6 w)	Recovery	[7]
12, M	Skull injury, fever, loss of consciousness	Frontal	NM	Craniotomy, drainage, bone defect restoration	CTRX (10 d) + VCM (43 d) + MNZ (12 d) + MEPM (12 d)	Recovery	[8]
6, F	Dental extraction, headache, fever, nuchal rigidity	Occipital	Emm1/T1	Aspiration	CTRX + MEPM	Seizure, visual field defect	[9]
3.5, M	Sore throat, fever, vomiting	Parietal	NM	Mastoid abscess	CTRX (10 d) + BPC (10 d) + CTX + CLDM	Hearing loss	[10]
7, F	Acute otitis media, fever, lethargy	Temporal	NM	NA	NA	NA	[11]
7, M	Tonsillitis, weakness, lethargy	Cerebellum	Emm9	Drainage	MEPM + CLDM + CTRX (52 d) + MNZ (10 d)	Recovery	[12]
3.5, F	Fever, vomiting, nuchal rigidity	Parietal	Emm1	Drainage	CTRX (52 d) + VCM + MNZ	Recovery	[12]
2.6, M	Fever, vomiting, lethargy	Along the temporal, parietal occipital border	Emm1	Drainage	CTRX (12 w)	Recovery	[13]
1.1, F	Upper respiratory tract infection, fever, vomiting, lethargy	Frontal	NA	Drainage	VCM + MNZ + CTX (7 d) + MEPM (6 w) + AMX (6 w)	Recovery	[13]
4, F	Acute otitis media, fever, extreme lethargy, vomiting	Temporal	Emm6	Drainage	CTX + VCM + MNZ CTRX (6 w) + AMX (6 w)	Recovery	[13]
2, F	Skin abscess, decreased muscle strength	Frontal	Emm22/ T46	Drainage	CXM + VCM (20 d) + MEPM (12 d) + LNZ (12 d)	Recovery	Present case

Abbreviations NM, not mentioned; CXM, cefuroxime; PCG, penicillin G; CAP, chloramphenicol; MNZ, metronidazole; AMX, amoxicillin; MEPM, meropenem; VCM, vancomycin; CTRX, ceftriaxone; BPC, benzylpenicillin; CLDM, clindamycin; CTX, cefotaxime; LNZ, linezolid; d, day; w, week

allergy, non-beta lactam antibiotics such as vancomycin or linezolid are preferred, which pass into the CSF better.This individualized approach to antibiotic therapy is designed to optimize clinical outcomes and to minimize the risks inherent to antibiotic resistance.

The patient's mild symptoms were probably due to the mild reaction between the pathogen and the host. On the one hand, the patient's immune deficiency might cause weak response to the pathogen. On the other hand, toxin-deficient bacteria could invade the host with increased intracellular persistence and decreased inflammatory response.

In this study, we found an undefined heterozygous mutation of *IRF8* (Pro166Leu) in the patient from her mother. To date, only a few studies reported that mutations in *IRF8* were associated with infectious disease, most of them focus on the biallelic mutation which leads to dysfunctional neutrophilia and monocytopenia, causing repeated even fatal infection [15, 16]. There were only 8 patients diagnosed with infectious disease due to *IRF8* heterozygous mutations. Heterozygous mutation at Thr80Ala ($n=2$) presented with disseminated infection after Bacillus Calmette-Guerin administration [17]; compound heterozygous mutation at Agr83Cys/ Arg291Gln ($n=1$) presented with repeated viral infectionc [15]; compound heterozygous mutation at Ala201Val/ Pro224Leu ($n=1$) presented with infectious mononucleosis caused by Epstein-Barr virus infection [18]; heterozygous mutations at Ala201Val ($n=1$), Thr96Met ($n=1$), and Gly139Ser ($n=1$) presented with pulmonary nontuberculous mycobacterial disease [18]; heterozygous mutations at Ala179Val ($n=1$) presented with disseminated nontuberculous mycobacterial disease [18]. No *IRF8* (Pro166Leu) heterozygous mutation-related disease has been reported. One pedigree study showed that the sister and brother who had a single heterozygous mutation (Ala201Val or Pro224Leu) of the patient (Ala201Val/ Pro224Leu) had a similar but mild history of infection and hospitalization [18]. However, no immune deficiency history of infection and hospitalizations was declared by the patient's mother who has the same *IRF8* heterozygous mutation. Whether the heterozygous mutation Pro166Leu in *IRF8 is* consistently related to the decreased immune function requires further investigation.

The *emm* gene encoded major virulence factor M protein was also the epidemiological typing tool of *Streptococcus pyogenes*. It has been reported that emm1, emm28, emm3, and emm12 were the top four common causes of severe invasive GAS infection [7]. Based on the previous research, 50% (4/8) cases were caused by emm1 [9, 12–14]. The isolate in this study was *Streptococcus pyogenes*. emm22/ST46, which was uncommon in China and never reported to be associated with pediatric GAS brain abscesses before. Based on the genome sequence analysis, we found this isolation lacked the *hasABC* hyaluronic acid capsule biosynthesis genes. It was similar to other reported emm22 strains which didn't produce the detectable hyaluronic acid capsule [19]. There was a broad consensus among researchers that hyaluronic acid capsules were required for producing invasive infections. However, the GAS brain abscess case we presented here supported the point that GAS emm22 lost capsules but retained the ability to cause sterile-site infections.

In conclusion, the GAS brain abscess was a rare invasive disease. However, the case we presented here reminded us that this infection has occult clinical manifestations. Our case supported previous findings that a satisfactory prognosis can be obtained after prompt surgical abscess drainage and appropriate antibiotic treatment.

Abbreviations

GAS	Group A *Streptococcus*
MRI	Magnetic resonance imaging
IRF8	Interferon regulatory factor-8
CSF	Cerebrospinal fluid
WBC	White blood cell
CRP	C-reactive protein
ST46	Sequence type 46
NM	Not mention
CXM	Cefuroxime
PCG	Penicillin G
CAP	Chloramphenicol
MNZ	Metronidazole
AMX	Amoxicillin
MEPM	Meropenem
VCM	Vancomycin
CTRX	Ceftriaxone
BPC	Benzylpenicillin
CLDM	Clindamycin
CTX	Cefotaxime
LNZ	Linezolid

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Author contributions

HCZ, SZP, ZMM, and SQ conceptualized and designed the study. HCZ and SZP treated the patient and drafted the initial manuscript. ZMM analyzed the result of bacterial whole-genome sequencing. LC, BGN, GWZ, XYP, ZJS, and HWL wrote sections of the manuscript. HWL and SQ coordinated the whole study and critically reviewed the manuscript for important intellectual content. All authors contributed to the manuscript revision, read, and approved the submitted version.

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Data availability

The complete genome sequence has been deposited in NCBI GenBank under accession number PRJNA835576 (BioProject) and Chromosome CP097251 (GenBank).

Declarations

Ethics approval and consent to participate

Study approval and ethical clearance were obtained from the Children's Hospital, Zhejiang University School of Medicine. Written informed consent was obtained from the guardian of the child and all the participants for participation before data collection. All methods were performed following the ethical standards as laid down in the Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent for publication

Written informed consent was obtained from the guardian of the child and all the participants for publication of medical images were taken from the patient.

Competing interests

The authors declare no competing interests.

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