A case report of *Salmonella* meningitis in three Chinese children and a literature review

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Case Report

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Abstract

Background: *Salmonella* is a common pathogen for gastroenteritis, but it rarely causes intracranial infection in China. To improve the understanding of pediatric *Salmonella* meningitis, we report three cases of *Salmonella* meningitis in Chinese children.

Case presentation: The patients were aged from 1 day to 14 months. Fever was the first symptom in two patients, while loose stool with a little mucus occurred in one patient during the course of disease. Peripheral white blood cell count, neutrophils count, and C-reactive protein were 20.08 - 25.2 $*10^9$/L, 15.4 - 19.7 $*10^9$/L, and 1.6 - >160 mg/L, respectively. CSF analysis showed that white blood cell count, glucose, and protein were 70 - 1473 $*10^6$/L, 0.18 - 3.19 mmol/L, and 598.1 - 6639.0 mg/L, respectively. Three isolates of *Salmonella* were detected in cerebrospinal fluid cultures, including *Salmonella* newport, *Salmonella* paratyphi, and *Salmonella* typhimurium (one case per each). All strains were sensitive to ceftriaxone, ceftazidime, cefoperazone / sulbactam, meropenem, and imipenem, while one strain was resistant to ampicillin. The blood cultures were all negative. All patients were treated with carbapenems after failed therapies of cefotaxime or ceftriaxone, for a total duration of 3 - 5 weeks. One patient died, and subdural effusion occurred in one of the two survivors.

Conclusions: *Salmonella* meningitis was rare, but the clinical conditions were serious. Carbapenems might be the first choice for treating *Salmonella* meningitis.

Background

As a common zoonotic disease, *Salmonella* infection is mainly transmitted by the fecal-oral route through contaminated food or water and causes acute gastroenteritis, typhoid, paratyphoid, bacteremia, and sepsis [1, 2], but rarely meningitis. Reports on *Salmonella* meningitis are mainly in developing countries, especially in Africa [3–6], but few in China. As a result, there is not enough clinical experience in the diagnosis and treatment of *Salmonella* meningitis in Chinese children. Therefore, we conducted this study to improve the condition. In our study, three cases were found to be *Salmonella*-positive in cerebrospinal fluid (CSF) cultures obtained from 2007 to 2019 according to the records in the laboratory information system of our hospital. The clinical characteristics and hospital course of these patients were collected from the medical records retrospectively and reported as follows. Additionally, relevant literatures were reviewed as well.

Case Presentation

Case 1

A 1 day-old premature infant, diagnosed as neonatal asphyxia and low birth weight, was admitted on November 6, 2018 for 4 hours after the asphyxia rescue. She was delivered by cesarean section in a local hospital at the gestational age of 33 weeks, with a birth weight of 1.55 kg and an Apgar score of 6–9

points / 1–5 minutes. After birth, she was treated with oxygen inhalation, sputum suction, and intravenous administration of penicillin and cefotaxime (the details were unknown). Her mother was a healthy rural woman who denied the history of unclean diet, diarrhea, or vomiting. On admission, physical examination and routine blood test revealed no abnormality except hypotonia. She was fed with formula milk after admission. Continuous fever occurred on the 8th day. CSF culture was performed on the 11th day and *Salmonella* typhimurium, a strain sensitive to ceftriaxone, ceftazidime, cefoperazone/sulbactam, and meropenem, but resistant to ampicillin, was isolated 5 days later. No gastrointestinal symptoms or neurological signs were noted during the hospitalization. The stool routine test was normal. The blood culture was negative while stool culture was not performed. The hospital course is shown in Fig. 1. The cerebral magnetic resonance image (MRI) is shown in Fig. 2. She was discharged after 32 days of hospitalization. No neurological sequelae had occurred up to July, 2020.

Case 2

A 44 day-old rural female infant was admitted on September 27, 2016 with the presentation of recurrent fever for 10 days. She was previously admitted to a local hospital for neonatal hypoglycemia, hyperbilirubinemia, and anemia, where she was bottle-fed, treated with piperacillin/tazobactam (the details were unknown), and discharged in stable condition after one month of hospitalization. On September 17, 2016, two days after discharge, she developed a fever (the temperature was not measured). On the next day, she was taken to a local hospital, where she was diagnosed with purulent meningitis, sepsis, septic shock, metabolic acidosis, liver dysfunction, and anemia, and was successively treated with cefotaxime, penicillin, ceftriaxone, meropenem, and vancomycin for a week (the details were unknown). However, the symptom improved while fever persisted, and then the parents took her home by abandoning therapy. Three days before admission to our hospital, she presented less eating, less crying, and less movement. One day prior to admission, she had a generalized tonic-clonic seizure that lasted for about 10 minutes and recovered spontaneously. History of unclean diet was denied, and no diarrhea or vomiting occurred during the course of disease. On admission, she was conscious, but her mental state was poor. The anterior fontanel was flat, and the neck was supple. Brudzinski's and Kernig's signs were negative, while Babinski's sign was positive. Stool routine test was normal. Blood culture was negative. Cultures of both CSF and stool specimens yielded *Salmonella* paratyphi of the same antibiogram which was sensitive to ampicillin, ceftriaxone, ceftazidime, cefoperazone/sulbactam, and meropenem. After admission, she had recurrent fever and convulsions, mild neck stiffness, and bulging anterior fontanel along with gradually deteriorated condition. Sudden cardiac and respiratory arrest occurred on the 15th day after admission, and the parents decided to give up all treatment and took her home. The hospital course is shown in Fig. 3. Follow-up by telephone confirmed her death. The cerebral MRI is shown in Fig. 4.

Case 3

A previously healthy 14-month-old urban girl was admitted on June 10, 2008 with a history of recurrent fever and sleepiness for half a month. The fever was continuous and high-grade up to 39.4 °C even after

10 days' treatments of intravenous penicillin, cefotaxime, and azithromycin administration in another hospital (the details were unknown). Neither the child nor any family members had a history of unclean diet, diarrhea, or vomiting, but she had loose stool with a little mucus during the hospitalization. On admission, she was conscious, irritable, the anterior fontanel was bulging, the neck was mild stiff, Brudzinski's and Kernig's signs were negative, and Babinski's sign was positive. Routine tests of the stool samples were all normal. *Salmonella* newport, which was sensitive to ampicillin, ceftriaxone, ceftazidime, cefoperazone/sulbactam, and meropenem, was found to be positive in CSF culture. Blood culture was negative. Stool culture was not performed. Considering the poor effect of antibiotic therapy and the presence of subdural effusion on computerized tomography (CT) scans, she was then treated with surgical drainage on the 9th day of hospitalization. During the operation, xanthochromic and slightly cloudy CSF was observed. She defervesced on the 12th day of hospital stay. The subdural drainage tubes were removed successively when her condition improved. She was discharged after 21 days of hospitalization. However, She was lost to follow-up after discharge. The hospital course is shown in Fig. 5. The cerebral CT images before and after the operation are shown in Fig. 6.

Discussion And Conclusions

Salmonella meningitis is a relatively rare clinical entity. Only three cases of *Salmonella* meningitis were diagnosed in our hospital in the recent 13 years. Consistent with the previous reports [1, 7–8], the patients were all young children. *Salmonella* is mainly transmitted by the fecal-oral route and contaminated food or carriers are the common sources of infection. Therefore, the gastrointestinal tract is often the first site of infection [9]. In this study, two cases were infants who were both bottle-fed in the neonatal period due to hospitalization. It was unclear that whether contaminated milk or bottles were the sources of infection, because no outbreak occurred among the hospitalized neonates during the same period in the hospital. Stool culture revealed the presence of *Salmonella* in one case who had no diarrhea, suggesting that *Salmonella* could cause invasive infection without obvious gastrointestinal symptoms in young infants [10]. Generally, *Salmonella* meningitis follows invasion of the bloodstream by *Salmonella* that passes through the intestinal mucosal and lymphatic barrier [9]. Negative results of blood culture might be related to the use of antibiotics before specimen collection, while the bacteria in bloodstream were easier to be killed and eliminated than those in the central nervous system.

No specific features are found in the routine and biochemical tests of CSF in *Salmonella* meningitis, neither do the symptoms nor signs. The younger the children, the more atypical their clinical manifestations. Therefore, the diagnosis of *Salmonella* meningitis mainly depends on CSF culture, while cultures of blood, stool, bone marrow, and other specimens are valuable for facilitating its diagnosis. Since the gastrointestinal tract is always the first site of *Salmonella* infection, stool culture is recommended for patients with suspected invasive infections caused by *Salmonella*. Unfortunately, two cases failed to perform stool culture in our study. So far, over 2700 serotypes of *Salmonella* have been described worldwide. The three serotypes detected in our study were newport, paratyphoid, and typhimurium, which were among the most common serotypes that cause invasive infections [11–13].

Prompt use of targeted antibiotics with adequate dosage and duration plays a significant role on prognosis [14–15]. In recent years, more and more *Salmonella* strains are resistant to ampicillin [16–18] while their sensitivities to ceftriaxone are still relatively high [19–21], and almost all of them are sensitive to carbapenems [19, 22]. Therefore, the third-generation cephalosporins (like ceftriaxone) are good choices for empirical treatment of *Salmonella* meningitis, and carbapenems may be considered for those with poor efficacy [20, 22]. Though the *Salmonella* strains detected in our study were all sensitive to ceftriaxone in vitro, the clinical effects were poor. It might be due to the fact that the patients' conditions were critical and that antibiotics were frequently changed before identification of the pathogens. However, antibiotics against gram-positive bacteria were still used in combination with carbapenems in two patients even after *Salmonella* were identified, suggesting that some clinicians had a lack of understanding of the antimicrobial therapy for *Salmonella* meningitis or over-considered the mixed infection with gram-positive cocci. On the other hand, regardless of the pathogens, good therapeutic effects could not be achieved when serious intracranial complications occur in patients with *Salmonella* meningitis, even if the antibiotics in use are sensitive. Just like case 3 in our study, she had been treated with meropenem, but the symptoms improved only after the surgical treatment of subdural effusion. We speculated that the most important reason for the poor therapeutic effect was the complication of subdural effusion rather than meropenem resistance. Honestly, the antibiotics treatment for this patient was unreasonable in the study, which was related to the fact that she was hospitalized more than ten years ago and the understanding of *Salmonella* meningitis was insufficient at that time. For case 2, CSF culture grew *Salmonella* three days after discontinuation of one-week treatment of meropenem, suggesting that the patients with inadequate duration of treatment were prone to relapse [20]. The conditions of patients with *Salmonella* meningitis are always serious, and the mortality can be as high as 30%-72% [8, 23–29]. As seen in the outcomes of the three patients in this study, neurological complications (e.g. seizure, hydrocephalus, subdural effusion) and sequelae (e.g. mental retardation, cerebral palsy, visual and hearing impairment) can be left even after treatments, which was consistent with previous reports [25, 30–31].

We were aware of the several limitations in our study: (i) it was a single-center study with a small sample size; (ii) the time span was long; (iii) there were some irrationalities in the selection, replacement, or combined application of antibiotics. Since the pathogens are unidentified in most patients with purulent meningitis by CSF culture for its low positive rate [32–33], the three cases of *Salmonella* meningitis diagnosed by CSF culture are probably not all the patients within the research period. In the future, more cases of *Salmonella* meningitis may be diagnosed if more advanced methods, such as bacterial nucleic acid detection in CSF, can be performed routinely.

Abbreviations

CSF: cerebrospinal fluid; MRI: magnetic resonance image; CT: computerized tomography; CBC: complete blood count; wbc: white blood cell; n: neutrophils; glu: glucose; pro: protein; LP: lumbar puncture; SP: subdural puncture.

Declarations

Ethical Approval and Consent to participate: This study was approved by the Ethics Committee of Children's Hospital of Zhejiang University (ID 2020-IRB-090).

Consent for publication: Written informed consents for publication of the clinical details were obtained from the parents of the patients.

Availability of supporting data: All data relating to this study are presented within the manuscript. Other materials are available from the corresponding author upon reasonable request.

Competing interests: All authors of this manuscript declare no competing interests.

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Authors' contributions: Jingli Zhao collected and analyzed the data, and wrote the original draft; Chunzhen Hua designed the study, developed the methodology, supervised the research and critical reviewed and edited the manuscript. Mingming Zhou, Hongjiao Wang, Yongping Xie and Gaoliang Wang contributed to data collection and editing of the manuscript. All authors read and approved the final version of the manuscript. All authors agreed to submit and publish the manuscript.

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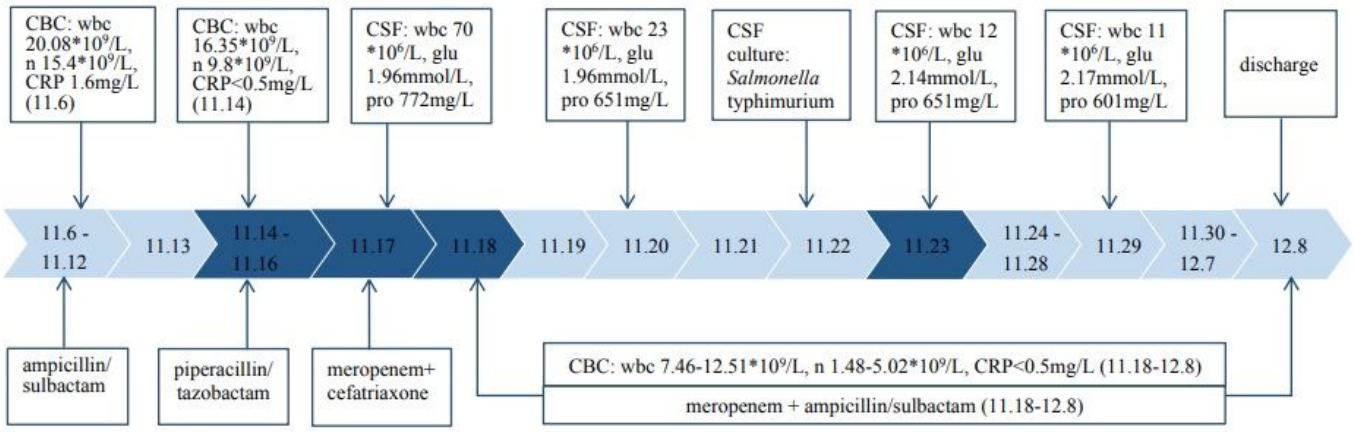
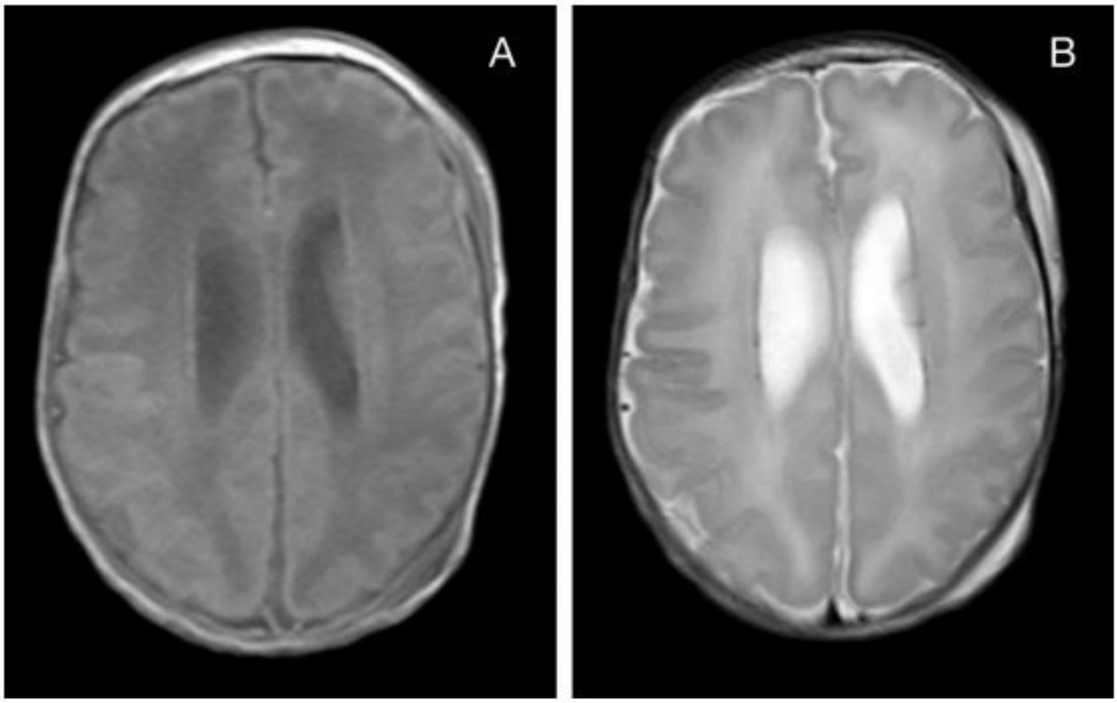
Figures



Note: ▶ : with fever (the highest temperature was between 37.7-38.4℃); ▶ : no fever; CBC: complete blood count; wbc: white blood cell; n: neutrophils; CSF: cerebrospinal fluid; glu: glucose; pro: protein. Dosage of antibiotics: ampicillin/sulbactam 100mg/kg/day; piperacillin/tazobactam 150mg/kg/day; meropenem 120mg/kg/day; cefatriaxone 100mg/kg/day.

Figure 1

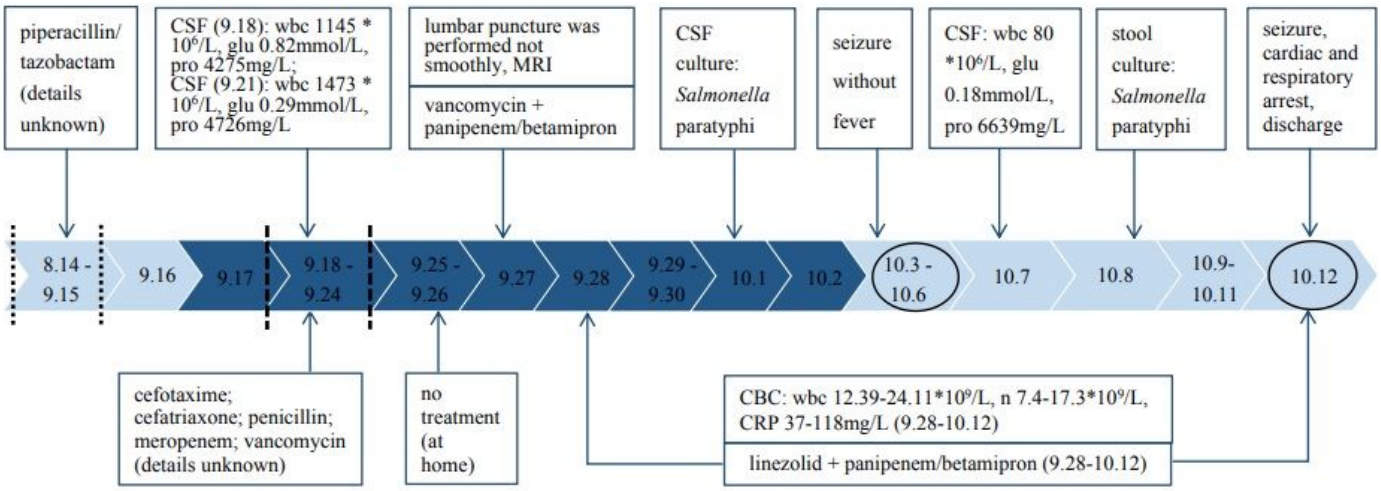
The hospital course of case 1



Note: On the 25th day of admission, T1 (A) and T2 (B) images of cerebral MRI showed high water content in white matter and dilatation of bilateral lateral ventricles.

Figure 2

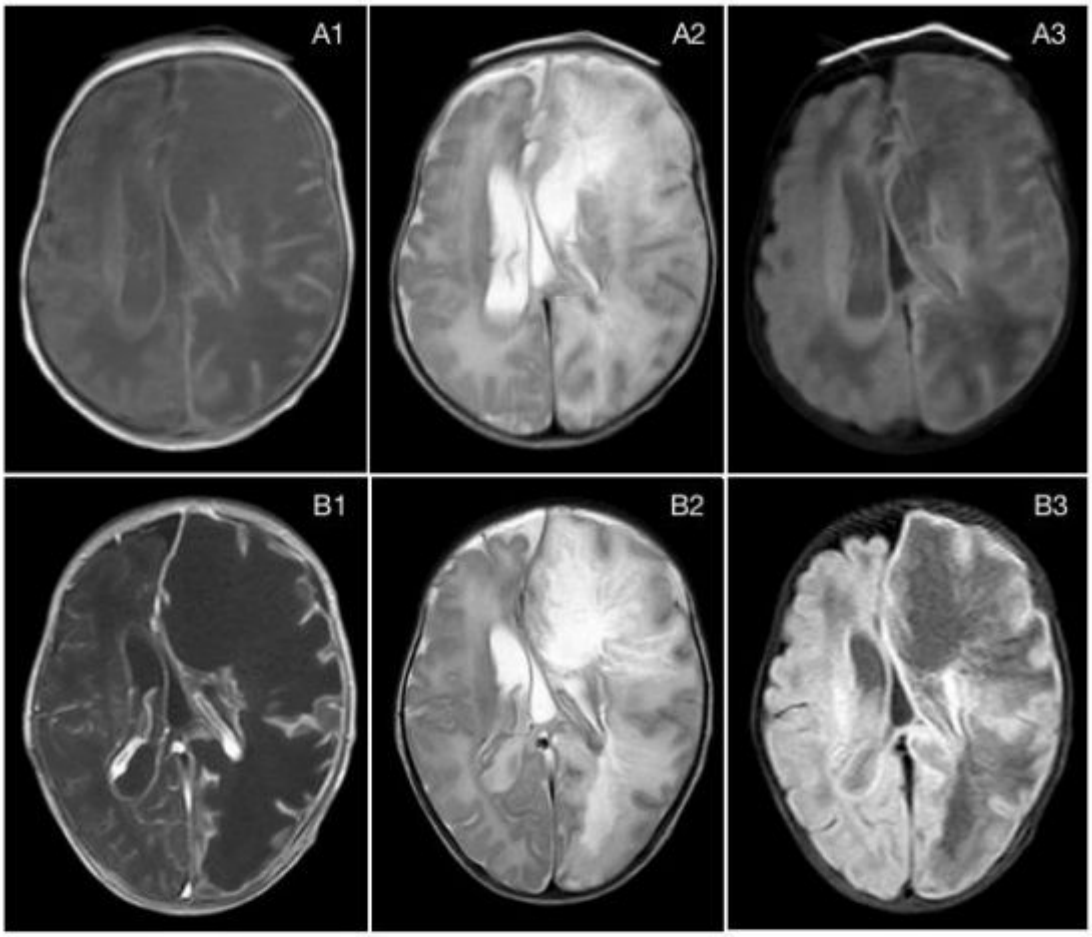
Cerebral MRI images of case 1



Note: : with fever (the highest temperature was 38.2-38.8℃); : seizure without fever; : no fever or seizure; : the first time of hospitalization in another hospital (8.14-9.15); : the second time of hospitalization in another hospital (9.18-9.24); CBC: complete blood count; wbc: white blood cell; n: neutrophils; CSF: cerebrospinal fluid; glu: glucose; pro: protein. The lumbar puncture on 9.27 was performed not so smoothly, and the CSF specimen was submitted only for culture but no routine and biochemical tests. Dosage of antibiotics: vancomycin 60mg/kg/day; panipenem/betamipron 90mg/kg/day; linezolid 30mg/kg/day.

Figure 3

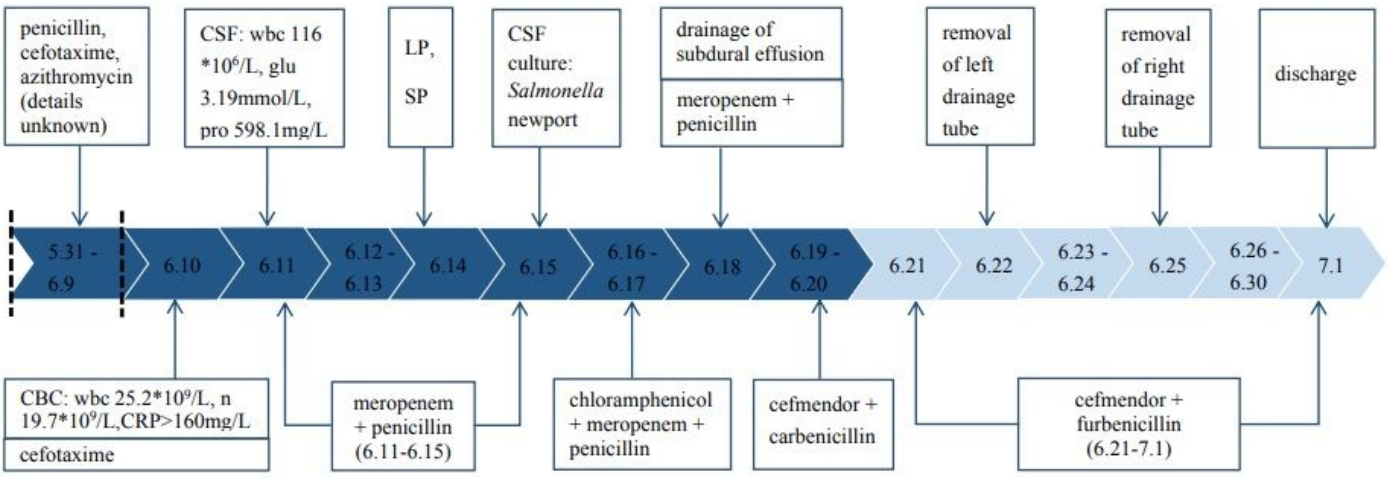
The hospital course of case 2



Note: A: On the 1st day of admission, T1 (A1), T2 (A2) and Flair (A3) images of cerebral MRI showed brain edema, tendency of extensive encephalomalacia in the left hemisphere, dilatation of bilateral lateral ventricles and the third ventricle, and right deviation of midline structure; B: On the 4th day of admission, T1 enhanced (B1), T2 (B2) and Flair (B3) images of cerebral MRI showed the lesions mentioned above were more significant.

Figure 4

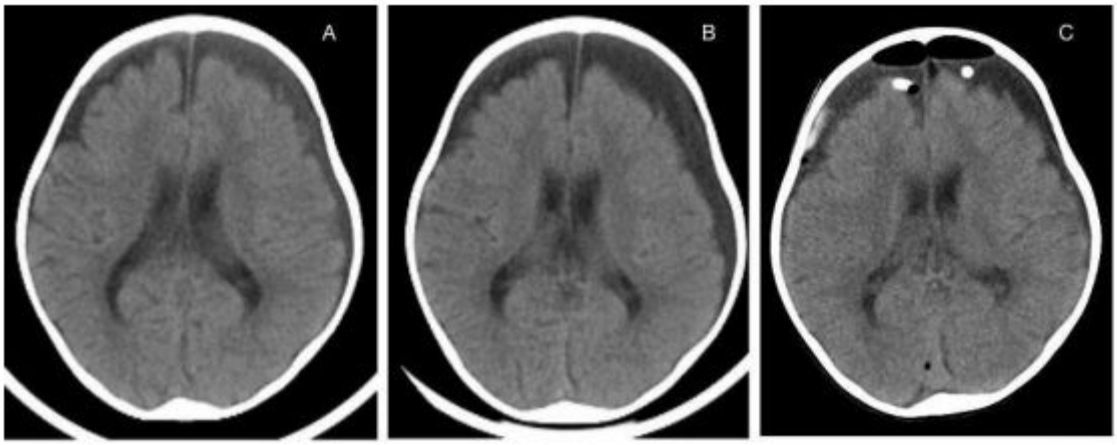
Cerebral MRI images of case 2



Note: : with fever (the highest temperature was 38.3-39.4℃); : no fever; : hospitalization in another hospital (5.31-6.9); LP: lumbar puncture; SP: subdural puncture; CBC: complete blood count; wbc: white blood cell; n: neutrophils; CSF: cerebrospinal fluid; glu: glucose; pro: protein; routine and biochemical tests (6.14) showed wbc $10*10^6$/L, glu 3.14mmol/L, pro 276.5mg/L in CSF from LP and wbc $20750*10^6$/L, glu 0.32mmol/L, pro 4782.8mg/L in fluid from SP, respectively. Dosage of antibiotics: cefotaxime 100mg/kg/day; meropenem 45mg/kg/day; penicillin 300,000IU/kg/day; chloramphenicol 30mg/kg/day; cefmendor 100mg/kg/day; carbenicillin 100mg/kg/day; furbenicillin 100mg/kg/day.

Figure 5

The hospital course of case 3



Note: A: On the 2nd day of admission, CT scan showed that the extra brain space was widened and the sulcus was obvious; B: On the 6th day of admission, CT scan showed subdural effusion (18mm diameter) and the sulcus was not obvious; C: On the 2nd day after subdural effusion drainage, CT scan showed that the subdural effusion was less than before.

Figure 6

Cerebral CT images of case 3