

Predisposing Conditions and Etiology of Pediatric Recurrent Bacterial Meningitis in Beijing Children's Hospital, 2006-2018

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Research article

Keywords:

Posted Date: March 4th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-15970/v1>

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Abstract

Objective To investigate the predisposing conditions, etiology and clinical characteristics of recurrent bacterial meningitis (RBM) in children.

Methods Seventy patients of RBM treated in Beijing Children's Hospital from January 2006 through December 2018 were retrospectively analyzed.

Results Predisposing conditions of RBM include: inner ear malformations 24(34.3%), dermal sinus tracts 15(21.4%), head trauma 15(21.4%), meningoencephalocele 12(17.1%), and immune deficiency 4(5.7%). Sixty-seven occasions of meningitis had positive bacterial cultures. Thirty-one occasions of *Streptococcus pneumoniae* (*S. pneumoniae*) meningitis and 3 occasions of *Haemophilus influenzae* type b (Hib) meningitis occurred in the 24 patients with inner ear malformations; Seventeen occasions of *S. pneumoniae* meningitis occurred in the 15 patients with head trauma, while 8 occasions of *S. pneumoniae* meningitis in 12 patients with Meningoencephalocele; There were 2 *Enterococcus faecalis* meningitis, 1 *Escherichia coli* meningitis and 1 *Staphylococcus aureus* meningitis in 15 patients with dermal sinus tracts; Two of 4 patients with immune deficiency suffered *S. pneumoniae* meningitis.

Conclusions Predisposing conditions of RBM in children include inner ear malformations, head trauma, meningoencephalocele, dermal sinus tracts, and immune deficiency. The most common etiology of RBM with inner ear malformation, head trauma, meningoencephalocele, and immune deficiency is *S. pneumoniae* . Empiric antibiotic treatment of RBM in children should cover *S. pneumoniae*.

Introduction

Bacterial meningitis in children can cause serious complications and neurologic sequela, causing great harm to children's health (Edmond et al., 2010; Stockmann et al., 2013). Children with predisposing conditions can develop recurrent bacterial meningitis (RBM). The early diagnosis of any underlying pathology is crucial to prevent further episodes. There were some case series and reviews about RBM (Tebruegge et al., 2008), but there was few about RBM in children with various underlying pathology. In this paper, the predisposing conditions and etiology of RBM admitted to Beijing Children's Hospital from January 2006 through December 2018 were summarized.

Methods

Study population

Seventy patients with RBM treated in Beijing Children's Hospital from January 2006 through December 2018 were retrospectively analyzed.

The diagnostic criteria for RBM must meet any of the following: (1) two or more episodes of meningitis caused by a different bacterial organism; (2) a second or further episode caused by the same organism

with a greater-than-3-week interval after the completion of therapy for the initial episode; (3) two or more episodes of bacterial meningitis (meet the criteria for clinical diagnosis of bacterial meningitis) if the episodes occurred a minimum of 3 weeks apart.

The diagnostic criteria of bacterial meningitis was based on the recommended case definition of the World Health Organization (WHO, 2003): (1) a sudden onset of fever ($> 38.5^{\circ}\text{C}$ rectal or $> 38.0^{\circ}\text{C}$ axillary); (2) one of the following symptoms or signs: headache, meningeal irritation, or altered consciousness; (3) cerebrospinal fluid (CSF) examination showing either of the following: leukocytosis ($> 100 \times 10^6$ cells/l) or leukocytosis ($10\text{--}100 \times 10^6$ cells/l) with an elevated protein (> 100 mg/dl) or decreased glucose (< 40 mg/dl); (4) positive culture, positive Gram stain, or positive bacterial antigen in the CSF. A case meeting diagnostic criteria 1, 2, and 3 at the same time was considered a probable case. A probable case meeting criterion 4 was considered a confirmed case.

Ethics analysis

This study was reviewed and approved by the Ethics Committee of Beijing Children's Hospital Affiliated to Capital Medical University.

Statistical analysis

Normal distribution data are described by mean \pm standard deviation (range), and non-normal distribution measurement data are described by median (range).

Results

Demographic data

Of the 70 cases, 41 were male and 29 were female. Their age at diagnosis was 1.2–16 years, with a median age of 6.2 years, and the 25th and 75th percentiles were 2.5 years and 8.3 years old, respectively.

Predisposing conditions, etiology and clinical manifestations

Predisposing conditions of 70 cases of RBM includes 24 (34.3%) cases of inner ear deformity, 15 (21.4%) cases of dermal sinus tracts, 15 (21.4%) cases of head trauma, 12 (17.1%) cases of meningoencephalocele, and 4 (5.7%) cases of immunodeficiency. A total of 168 episodes of bacterial meningitis occurred in 70 patients. (Fig. 1)

Nineteen of 24 patients who had inner ear malformation were unilateral malformations, whereas other 5 patients were bilateral malformations. In these 24 patients, the average age of correct diagnosis was 3.1 (1.3–9.2) years old and bacterial meningitis occurred 2–4 times before correct diagnosis. In 15 patients who had history of head trauma, the median time from head trauma to the first episode of bacterial meningitis was 2 months (3 days–1 year 8), and there were 2–4 episodes of bacterial meningitis for each patient. The average age of correct diagnosis and surgical treatment was 6.2 (3.4–11) years in 12 patients with meningoencephalocele, and they each suffered 2–3 episodes of bacterial meningitis. Sixty percent of patients with history of head trauma and 41% of patients with meningoencephalocele have the

symptoms of cerebrospinal fluid leakage. There were 15 patients with dermal sinus tracts, eight of whom were lumbosacral dermal sinus tracts, four with occipital dermal sinus tracts, and other 3 with chest dermal sinus tracts. There were 2–3 episodes of bacterial meningitis for each patient with dermal sinus tracts. Four patients were diagnosed with immunodeficiency, including 3 agammaglobulinemia and 1 IgG2 subclass deficiency. They each suffered with 2–3 episodes of bacterial meningitis. (Table 1)

Sixty-seven episodes had positive bacterial cultures, including 58 *Streptococcus pneumoniae* (*S. pneumonia*), 4 *Haemophilus influenzae* type b (*Hib*), and 2 *Enterococcus faecalis* (*E. faecalis*), 1 *Escherichia coli* (*E. coli*), 1 *Streptococcus viridans*, and 1 *Staphylococcus aureus*. (Fig. 2)

Sixty-seven occasions of meningitis had positive bacterial cultures. Thirty-one occasions of *Streptococcus pneumoniae* (*S. pneumonia*) meningitis and 3 occasions of *Hib* meningitis occurred in the 24 patients with inner ear malformations; Seventeen occasions of *S. pneumonia* meningitis occurred in the 15 patients with head trauma, while 8 occasions of *S. pneumonia* meningitis in 12 patients with Meningoencephalocele; There were 15 cases of dermal sinus tracts, 2 of which had *E. faecalis* meningitis and 1 case had *E. coli* meningitis. Immune deficiency was diagnosed in 4 cases, 2 of which had *S. pneumoniae* meningitis. (Table 1).

TABLE 1 Predisposing Conditions and Etiology of Recurrent Bacterial Meningitis

Condition	Total no. of cases	Median years of age	Organism(s) isolated (no. of occasions)
Inner ear malformations	24	3.1 (1.3-9.2)	<i>S. pneumonia</i> (31) <i>H. influenzae</i> (3)
Dermal sinus tracts	15	2.1 (1.2-8)	<i>E. faecalis</i> (2) <i>E. coli</i> (1) <i>S. aureus</i> (1)
Head trauma	15	8.5 (2-16)	<i>S. pneumonia</i> (17) <i>S. viridans</i> (1)
Meningoencephalocele	12	6.2 (3.4-11)	<i>S. pneumonia</i> (8) <i>H. influenzae</i> (1)
Immune deficiency	4	5.5 (4.2-8.2)	<i>S. pneumonia</i> (2)

Discussion

The results of this study show that the common predisposing conditions of RBM in children are inner ear malformations, dermal sinus tracts, head trauma, meningoencephalocele. Children younger than 3 years old, especially infants younger than 1 year of age, are susceptible population for bacterial meningitis. Underlying conditions should be considered in children older than 3 years old who suffered bacterial meningitis. These conditions include basic anatomical deformities (inner ear deformities, meningoencephalocele), and history of head trauma, asplenia, immune deficiency, etc (Tebruegge et al., 2008). These underlying diseases are also the cause of RBM in children. Of course, infants and young children under 3 years of age who have these conditions can also suffer RBM. Our study showed that

congenital anatomic deformities, including inner ear deformities, dermal sinus tracts and meningoencephalocele, accounted for 76.1% of the predisposing conditions of RBM, followed by 16.9% of head trauma. Congenital or acquired anatomical abnormality should be firstly considered in children with RBM.

Our study showed that 79.2% of the inner ear malformations were unilateral malformations. Hearing abnormalities in patients with unilateral malformation were not easily detected by parents or doctors, resulting in delayed diagnosis and treatment. Majority of inner ear malformations could not be correctly diagnosed until one or even several episodes of bacterial meningitis (Lien et al., 2011). Malformation of the inner ear can be easily detected by routine hearing tests. Inner ear malformations in our study were all found by hearing tests, followed by temporal CT scan to make definite diagnosis. In addition, hearing loss is the most common complication and sequela of bacterial meningitis. Therefore, we recommend that all children with bacterial meningitis require routine hearing tests for monitoring the sequela of hearing loss, and also for the potential inner ear malformations.

Our study shows that dermal sinus tracts accounts for 21.1% of children with RBM. The dermal sinus tract is an abnormal development of the ectoderm during the embryonic period. Skin or epithelial tissue remains in the cranial cavity or spinal canal to form a skin-like or epithelial-like cyst. The dermal sinus tracts can often be found by physical examination. The most common site is the lumbosacral region in midspinal line, followed by the chest and occipital region in midspinal line. It is more difficult to find the dermal sinus tracts in occipital region which is covered with hair. So it is necessary to remove the hair during the physical examination, combined with imaging examination to make the right diagnosis. Therefore, RBM in children requires careful physical examination to determine the presence of dermal sinus tracts.

Our study showed that head trauma and meningoencephalocele accounted for 21.1% and 16.9% respectively in children with RBM. Sixty percent and 41% of the patients in these two groups had the symptoms of cerebrospinal fluid leak. So the possibility of skull anatomical defects cannot be excluded in children without symptom of cerebrospinal fluid leak. These patients may show intermittent cerebrospinal fluid leak, especially in case of increased intracranial pressure (such as sneezing) or in forward tilt position (Prosser et al., 2011; Mathias et al., 2016). The liquid is clear and has a salty or even sweet taste, which needs to be distinguished from allergic rhinitis (Ziu et al., 2012). The skull CT and MRI scan should be done for these patients to find the abnormalities (Connor, 2010). The time interval from head trauma to the first occurrence of bacterial meningitis ranges from 3 days to 1.7 years. Therefore, during the history taking of head trauma for RBM, it should not only be limited to history of days to months before the onset of the meningitis, but also the history of trauma years ago.

Our study showed that *S. pneumoniae* infection is the most common etiology of RBM in children, especially in patients with malformations of the inner ear, meningoencephalocele, head trauma, and innate immunodeficiency, with 62.5%, 46.7%, 66.7% and 50% of patients respectively had at least one episode of *S. pneumoniae* meningitis. *S. pneumoniae* is a common colonizing bacterium in the

respiratory tract and external ear canal followed by Hib. The anatomic defects of inner ear malformations, meningoencephalocele, and basic diseases of skull trauma result in the communication between the skull and the ear canal, or the nasal cavity or sinuses. Colonizing bacterium can easily invade the skull through local anatomic defects and causes meningitis (Ingels et al., 2014). The 4 patients of immunodeficiency in our study were all antibody-deficient. *S. pneumoniae* was also the most common etiology. Patients with antibody deficiency are prone to the infection of capsular bacteria (Winkelstein et al., 2006; Ingels et al., 2015; Lopez et al., 2017). *S. pneumoniae* is a typical capsular bacterium. For that *S. pneumoniae* is the most common cause of RBM in children, empirical antibiotic treatment of RBM in children should cover *S. pneumoniae*. In our patients with RBM, Hib is the second etiology only to *S. pneumoniae*. Patients with dermal sinus tracts had two episodes of *E. faecalis* meningitis, one episodes of *E. coli* meningitis, and one episodes of *Staphylococcus aureus* meningitis. Enterobacteriaceae, enterococci and *Staphylococcus aureus* should be considered as etiology of RBM in patients with lumbosacral dermal sinus tracts where the deficit is near the perineum, while *Staphylococcus aureus* meningitis is more common in patients with chest and occipital dermal sinus tracts.

In our study, the rate of positive cultures is low. Some patients had negative cultures, because they had received antibiotic treatment before blood or cerebrospinal fluid was got for culture. As the Implementing of antibiotic stewardship program in China, this problem will be solved.

In summary, predisposing conditions of RBM in children include malformations of the inner ear, dermal sinus tracts, head trauma, meningoencephalocele, and immune deficiency. *S. pneumoniae* is the most common etiology of RBM in children. Empiric antibiotic treatment should cover *S. pneumoniae*

Abbreviations

RBM: Recurrent bacterial meningitis; *S. pneumoniae*: *Streptococcus pneumoniae*; Hib: *Haemophilus influenzae type b*; *E. faecalis*: *Enterococcus faecalis*; *E. coli*: *Escherichia coli*; *S. aureus*: *Staphylococcus aureus*.

Declarations

Acknowledgements

We would like to thank the nurses and doctors working in the Department of Infectious Diseases, Beijing Children's Hospital, who provided medical services for these patients.

Funding

This work was supported by the Special Fund of the Pediatric Medical Coordinated Development Center of Beijing Hospitals Authority (No. XTZD20180501), the Beijing Hospitals Authority Dengfeng Talent

Training Plan (No. DFL20181201) and the Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (No. 2019XK320080).

Availability of Data and Materials

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

Authors' Contributions

All of the authors had access to the full dataset (including the figures and tables) and take responsibility for the integrity of the data and the accuracy of the data analysis. LG, CTM, CHY, HB, HHL, GX, GLY and LSY conceived and designed the study. LG, CTM, CHY, HB, HHL and GX collected the data and designed the analysis. LG, CTM and CHY interpreted the data. CTM wrote the first draft of the paper. Gang Liu and CTM reviewed and approved the final report.

Ethical Approval and informed consent

This study was reviewed and approved by the Ethics Committee of Beijing Children's Hospital Affiliated to Capital Medical University. Because this is a retrospectively study, we obtained the data of patients from the Medical Records and Statistics Room and we analyzed the data anonymously; thus, informed consent was not required.

Consent for Publication

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

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Figures

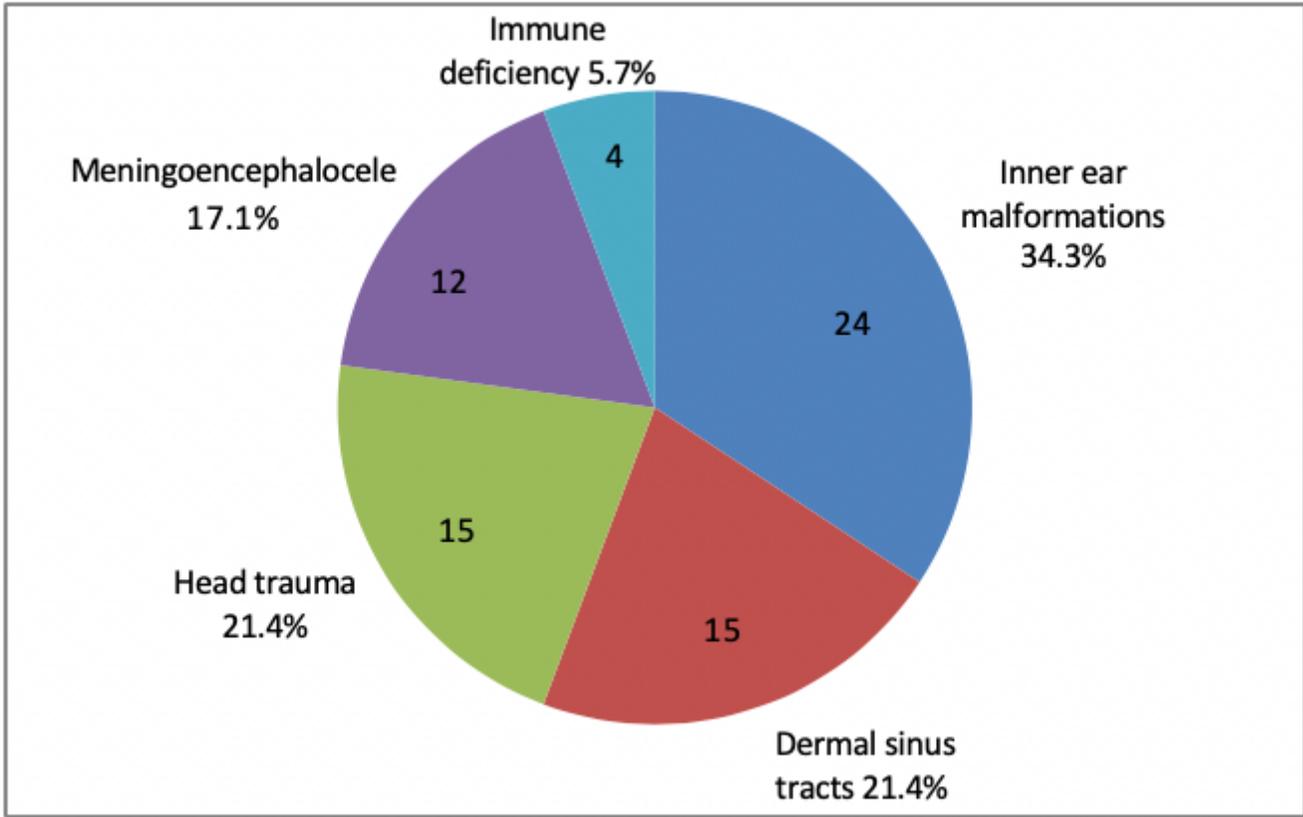


Figure 1

Underlying conditions predisposing to 70 patients with recurrent bacterial meningitis

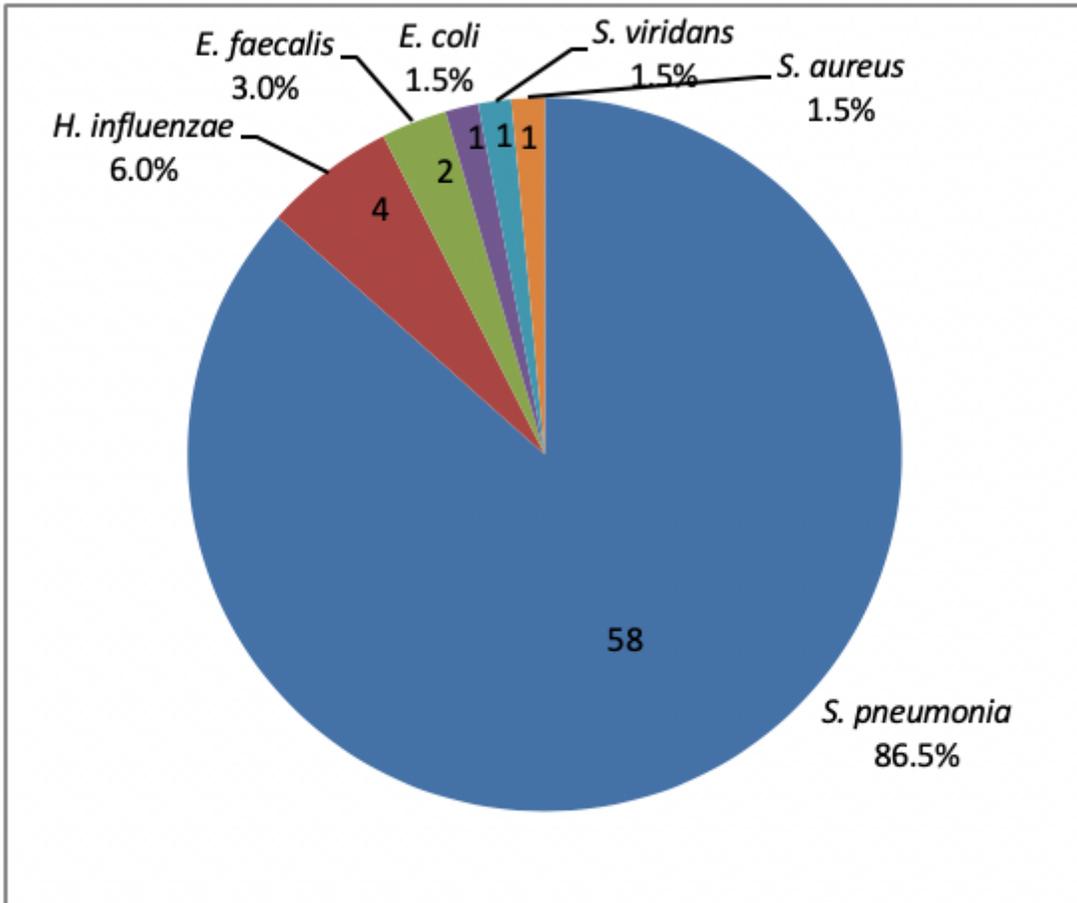


Figure 2

Causative bacteria isolated in recurrent bacterial meningitis