Recurrent bacterial meningitis in children: our experience with 14 cases

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Recurrent bacterial meningitis is an uncommon but life-threatening condition. The aim of this study was to evaluate the demographic, clinical, microbiological, and radiological features of recurrent bacterial meningitis in children. Fourteen patients (10 male, 4 female) treated for recurrent bacterial meningitis were reviewed. The mean age of the patients was 87 months (range: 6 months to 13 years). There were 67 episodes of meningitis documented in these 14 patients. Six patients had developmental anatomical defects, five had traumatic anatomical defects and three had primary immune deficiency diseases as predisposing conditions. We suggest that, in a case of recurrent meningitis, a pediatrician should question and examine the patient carefully in search of a possible anatomical defect or immunodeficiency. Vaccination and surgical treatment of the anatomical defects may be important.

Key words: children, recurrent, meningitis.

Acute bacterial meningitis is a potentially life-threatening infection of the cranial and spinal leptomeninges that can lead to significant mortality and morbidity[1]. Recurrent bacterial meningitis (RBM) is defined as any reappearance of clinical and laboratory signs and symptoms of bacterial meningitis after adequate and successful treatment of a preceding meningitis[2,3]. A single episode of bacterial meningitis in pediatric patients is usually the result of hematogenous dissemination of organisms from a distant site of infection. In recurrent episodes of meningitis, the other possible routes of bacterial invasion to the cerebrospinal fluid (CSF) should also be considered[1]. Developmental or traumatic defects may be responsible for RBM via access of bacteria into the subarachnoid space. An undiagnosed immunologic deficiency may allow the host to be susceptible to potential bacterial pathogens of meningitis. A fairly large number of possible predisposing factors were reported. Therefore, extensive diagnostic procedures should be performed to determine the predisposing conditions of RBM[2].

Herein, we aimed to present the demographical, clinical, microbiological, and radiological features of 14 consecutive pediatric cases with RBM.

Material and Methods

The Sami Ulus Children's Health and Diseases Training and Research Center in Ankara is one of the largest children's hospital in Turkey and serves as a reference pediatric center for the entire country. The Medical Center provides care to more than 20,000 inpatients and more than 200,000 outpatients annually. A review of medical reports of patients treated with RBM in our hospital between January 2004 and October 2008 was performed retrospectively. The patients were evaluated with history, physical examination, laboratory investigations, radiological imaging, and treatment outcomes. The diagnosis of acute bacterial meningitis was established according to the presence of a compatible clinical history, physical examination and CSF findings. CSF leukocyte count of >1000/mm^3 (predominantly polymorphonuclear cells), CSF glucose of <50% of blood glucose, CSF protein of >50 mg/dl and/or a positive CSF culture were regarded as bacterial meningitis[4]. A second episode of meningitis was considered as a recurrence if it was due to a different organism from the first organism or if it was due to the same organism but occurred more than three weeks after the completion of therapy for the initial episode[3]. Eight of the 14 patients with

RBM were diagnosed clinically, bacteriologically and/or according to laboratory results at our institution initially. The remaining six cases were referred to our institution for further management, after the diagnosis of acute bacterial meningitis was established elsewhere. Their diagnosis was also established by medical records. Patients with ventriculo-peritoneal shunts were excluded because the clinical, microbiological, diagnostic, and treatment features differ from acute bacterial meningitis. Immunological evaluations including absolute peripheral leukocyte and neutrophil counts, quantitative serum immunoglobulin (Ig) and IgG subclass levels, complement 3 and 4 levels, isohemagglutinin levels, and human immunodeficiency virus (HIV) antibody test were performed in all patients. Total hemolytic complement activity (CH50) test was not available in our center; therefore, only eight of the patients were tested for CH50.

Further immunological investigations were done when unusual microorganisms were cultured from the CSF. The patients with no history of trauma and with no evidence of CSF leakage also underwent advanced immunological investigations. Cranial computerized tomography (CT) was conducted on all patients. A CT scan of paranasal sinuses and temporal bones, cranial magnetic resonance imaging (MRI) and MR cisternography were performed in selected cases according to their clinical risk factors.

Results

The total number of acute bacterial meningitis cases in the study period was 128. Data from 14 of the 17 patients with RBM are presented because 3 cases with ventriculo-peritoneal shunts were excluded. After excluding the 6 cases who were referred, the institutional RBM rate was 6.2% (8 of 128), while our overall institutional RBM rate was 10.9% (14 of 128). The mean patient age was 87 months (range: 6-156 months). The mean follow-up was 19.5 months (range: 4-54 months). Of the 14 patients, 10 were male and 4 were female. The total number of meningitis episodes was 67, with a range of 2-20 episodes per patient. The etiology of RBM was a development defect in 6 patients, a traumatic anatomical defect in 5 patients and a primary immunological disorder in 3 patients. CSF rhinorrhea was detected in 3 patients with encephalocele, posttraumatic meningitis and Mondini dysplasia. Five patients had a history of trauma (3 had a motor or motorcycle accident, 1 had a history of falling from 2-story height and 1 had skewer penetration to the nose). The period between trauma and the first episode of meningitis varied from 12 to 114 months, with a mean of 38 months.

The causative agents of RBM were *Streptococcus pneumoniae* in 8 patients, *Salmonella typhi serotype enteritidis* in 1 patient and *Haemophilus influenzae* type *e* biotype 4 in 1 patient in a total of 28 episodes. In the remaining 39 episodes of meningitis, no organisms were grown in CSF. The number of isolated organisms of the patients are shown in Table I. *Salmonella typhi serotype enteritidis* and *Haemophilus influenzae* type *e* biotype 4 were detected in patients with interleukin-12 receptor β-1 (IL-12 Rβ1) deficiency and common variable immunodeficiency (CVID), respectively. No pathogen was cultured in the remaining 4 patients. Basic immunologic studies were all normal except in the patients with CVID and IgG2-G4 deficiency. CH50 tests were positive in 8 patients who were able to be tested. Eight of the 11 patients with developmental and traumatic anatomical defects were diagnosed by CT. However, patient nos. 3, 8 and 11 underwent MR cisternography as CT scans revealed no pathology contributing to the recurrent meningitis.

All of the patients were treated with a combination of ceftriaxone and vancomycin. When the culture results revealed ceftriaxone-susceptible *S. pneumoniae* or the other susceptible organisms, vancomycin was stopped. The cases with IgG2-G4 deficiency and CVID were also treated with intravenous immunoglobulin every 21 days. The case with IL-12 Rβ1 defect was treated with recombinant interferon gamma (rIFN-γ, Imukin, Boehringer-Ingelheim, 50 μg/m^2, 3 times a week subcutaneously) in addition to antibiotic therapy. None of the patients had prophylactic antibiotic treatment. All patients were vaccinated with non-conjugate pneumococcal vaccine and *H. influenzae* type b vaccine, depending on the patient's age. Five of six patients with developmental anatomical defects underwent corrective neurosurgical

Table I. Features of the Patients with Recurrent Bacterial Meningitis

No	Age (years)	Sex	No of episodes	Responsible organism /no of isolated microorganisms	Etiology	Surgical treatment	Outcome
1	13	M	2	*S. pneumoniae* / **2**	Trauma (fracture at left petrous bone)	No	Unknown
2	8	M	3	?	DD (encephalocele)	Yes	No meningitis episode for 3 years
3	13	M	5	?	DD (fistula between dura and sinus ethmoidalis)	Yes	No meningitis episode for 2 years
4	5	F	3	?	Trauma (defect on mastoid antrum)	Yes	No meningitis episode for 2 years
5	1.5	M	6	*S. typhi* / **3**	PID (IL-12 1βR defect)	No	Dead
6	12	M	20	*S. pneumoniae* / **9**	Trauma (fistula at anterior skull base)	Yes	Meningitis episodes persist, going on 4.5 years
7	2	F	5	*S. pneumoniae* / **2**	DD (Mondini dysplasia)	Yes	No meningitis episode for 3.5 years
8	8	M	2	*S. pneumoniae* / **2**	DD (fistula at cribriform plate)	No	No meningitis episode for 2 years
9	11.5	F	2	*S. pneumoniae* / **2**	Trauma (defect on mastoid antrum)	No	No meningitis episode for 2 years
10	0.5	M	2	*S. pneumoniae* / **2**	DD (encephalocele)	Yes	No meningitis episode for 1 year
11	9.5	M	2	*S. pneumoniae* / **1**	Trauma (fistula at anterior cribriform plate)	Yes	No meningitis episode for 9 months
12	1.5	M	4	?	DD (dermal sinus tract)	Yes	No meningitis episode for 9 months
13	8	F	9	*S. pneumoniae* / **4**	PID (IgG2-IgG4 deficiency)	No	Dead
14	9	M	2	*H. influenzae* / **1**	PID (common variable	No	No meningitis episode for 4 months

DD: Developmental defect. **PID:** Primary immunological disorder. IL: Interleukin.

operations. Neurosurgeons did not advise any surgical procedure to the remaining case of bony defect in the cribriform plate of the ethmoid bone (patient no. 8). He had no meningitis episode for 2 years. Three of five cases of traumatic anatomical defects were operated. From the total number of 8 patients who underwent neurosurgical operations, 7 of them were free of any recurrences as of the time of reporting. The remaining patient (no. 6) continued having meningitis episodes. The MR cisternography of this patient revealed ongoing fistula. Two cases with RBM died from IL-12 Rβ1 deficiency and IgG2-G4 deficiency at the sixth and ninth episodes of meningitis, respectively. Late complications of acute bacterial meningitis in the patients with RBM could not be evaluated as they had short-term and irregular follow-ups. The patient features are summarized in Table I.

Discussion

Recurrent bacterial meningitis is an uncommon condition in children. There have been relatively scarce reports concerning the incidence of recurrent meningitis. A review of 463 children with bacterial meningitis identified six patients with confirmed recurrent episodes, representing an incidence of 1.3% 5. In an adult study, Adriani et al.[6] estimated the annual incidence of RBM to be around 0.12 cases per 100,000 adults, an incidence of 5% of community-acquired bacterial meningitis episodes. Since our center provides care as a reference hospital, our institutional and overall institutional RBM rates were found to be noticeably high, at 6.2% and 10.9%, respectively. Most of the reports on RBM are composed of isolated case reports. Only 15 reports determined five or more cases, mostly belonging to the last decade[1-3,5,7-9]. Kline[10] reviewed the literature for 10 years and collected 47 pediatric and adult patients in 1989. Of these 47 patients, the underlying cause was immunodeficiency in 21% of cases; congenital, traumatic and surgical CSF fistula and unknown cause accounted for 74% and 6%, respectively. Immune system disorders are relatively uncommon but important causes of recurrent meningitis[11]. Recently, a comprehensive review on RBM was reported by Tebruegge and Curtis[3] in 2008. They identified 144 publications in the literature from 1998 to 2007. Based on their data, a total of 363 cases with RBM including both children and adults were reported. Of these 363 patients, the underlying cause was immunodeficiency in 132 (36%) cases, developmental anatomical defects in 112 (31%), traumatic defects in 102 (28%), and parameningeal infections in 17 (5%). In our patients, we found mostly developmental or traumatic anatomical defects as the underlying cause; no parameningeal infections were determined. Parameningeal infections are known to cause bacterial meningitis, but there is no case report of RBM due to parameningeal infection in children[3].

Developmental and traumatic anatomical defects are fundamental underlying causes of RBM. These conditions are mostly due to the presence of a communication of the subarachnoid space with the paranasal sinuses, nasopharynx, middle ear cavity, or skin. Fractures of the paranasal sinuses, cribriform plate and petrous bone can lead to communications with paranasal sinuses, nasopharynx, and middle ear cavity, respectively[11,12]. In these patients, meningitis may be recurrent and due to the possible direct contact of bacteria in these cavities, most commonly caused by *S. pneumoniae*[13]. In our series, *S. pneumoniae* was cultured from the CSF in 6 of the 11 cases of anatomical defects. CSF rhinorrhea or otorrhea is an important clue for determining the predisposing conditions for recurrent meningitis. Taking a detailed history and a comprehensive physical examination may enable realization of a CSF rhinorrhea. We had only three cases with rhinorrhea, all of whom were operated to prevent CSF leakage. Although CSF leakage may improve spontaneously after trauma, 10% to 20% of patients experience RBM. A greater associated risk has been reported when CSF leakage exists, in particular, if it persists for more than seven days[13]. In case of the existence of developmental or traumatic anatomical defects, a pediatrician needs neurosurgical or otolaryngological consultation to evaluate the necessity of surgical repair, which has an overall high success rate and low mortality and morbidity[6,7]. The interval between trauma and the first episode of meningitis is known to be variable from a few hours to many years [3,5,8]. In our series, the longest period was determined as 9.5 years. Therefore, detailed information about trauma history pertaining to infancy plays an important role in determining the predisposing factors for RBM.

Patients with congenital anatomical defects such as skull base defects, especially anterior localization, encephalocele, intracranial or intraspinal defects with or without a dermal connection, inner ear defects including Mondini dysplasia, neuroenteric fistula, and fibrous bone dysplasia are susceptible to RBM[11,14]. Of the inner ear defects, Mondini dysplasia is a developmental arrest characterized by hypoplasia of the cochlear labyrinth and is usually accompanied by sensorineural hearing loss with or without vestibular symptoms. This developmental defect can be associated with CSF leak and recurrent meningitis. An anatomical fistula between the inner ear and CSF is the main cause of meningitis in Mondini dysplasia[15]. It is reported that the first attack of meningitis can delay until school age, as in our patients with developmental anatomical defects[8].

Patients with immune disorders are at increased risk of RBM. Undiagnosed immune deficiency can enable the host defenses as inadequate barriers to potential bacterial pathogens[5]. Asplenia, X-linked agammaglobulinemia, selective decrease in IgG, IgA and IgG2 subclasses and deficiency of complement components (C3, C7, C8, C9) are well-known immune disorders leading to RBM[3,5,14]. CH50 has an important role in determining *late*-acting complement components[16]. In our study, as the CH50 test was applied in only 8 patients, a clear explanation of any deficiency of a component of complement can not be made. In addition to these causes, patients with defects of IL-12 IL-23/ IFN-γ axis are susceptible to weakly virulent non-typhoidal salmonella species septicemia and life-threatening infections, as in our case of *Salmonella typhi serotype enteritidis* meningitis[17].

Even if no other abnormality is found on the imaging studies except CSF leakage, basic investigations for immune deficiency should be considered before surgery. The two cases with recurrent *S. enteritidis* meningitis and pneumococcal meningitis who were diagnosed as primary immunological disorders died despite the appropriate treatments. To our knowledge, meningitis due to *H. influenzae* type *e* biotype 4 is an extremely rare pathogen[18], and only one case with RBM due to this microorganism was reported in the literature[19]. *S. enteritidis* may be a cause of meningitis in young infants, functional or anatomical asplenia, and defects of the IL-12 IL-23/ IFN-γ axis. However, recurrent *S. enteritidis* meningitis is rarely reported[17].

In RBM, imaging studies should include CT of the cranium, paranasal sinuses and temporal bones[5]. When these imaging methods remain insufficient, further imaging studies including CT cisternography or MR cisternography can be performed in selected patients. MRI scans offer the best definition of brain parenchyma and soft tissue, which is particularly important in the context of encephaloceles[3]. It is reported that MR cisternography has a higher detection sensitivity of CSF fistulas than CT cisternography[20]. Our three cases with CSF fistulas could be diagnosed using MR cisternography.

The use of prophylactic antibiotics remains controversial in patients with skull base defects and CSF fistulas[8,22]. A newly reported review showed that antibiotic chemoprophylaxis had no benefit in preventing the recurrence of meningitis in basilar skull fractures, whether or not there is evidence of CSF leakage[13]. Once antibiotic prophylaxis is commenced, it should be continued for many years with the risk of colonization by more resistant flora[19]. None of our patients underwent prophylactic antibiotic treatment. Vaccination against pneumococci, *H. influenzae* type b and meningococci is the mainstay of preventive treatment in cases of RBM[23]. However, there are questions about the efficacy of immunization in cases of RBM caused by anatomical defects[6,21]. Vaccination failed to prevent recurrence in our two cases with immunodeficiencies. On the other hand, vaccination might be efficacious in some patients with anatomical defects (patient nos. 8 and 9). Studies with large patient series with RBM can clarify this agreement.

In conclusion, in a case of RBM, a pediatrician should question and examine the patient carefully in search of a possible developmental or traumatic anatomical defect or immunodeficiency disease. Generally, excessive diagnostic and therapeutic procedures are indicated. A number of possible predisposing factors should be kept in mind before starting

the investigation for this rather rare condition. Appropriate vaccination and surgical correction of developmental or traumatic anatomical defects, when present, are considered to be important in a case of RBM, which may lead to crucial problems. In addition, RBM may be the first presentation of a primary immunodeficiency disorder.

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