Diagnostic Approach to Recurrent Bacterial Meningitis in Children

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Recurrence of bacterial meningitis in children is not only potentially life-threatening, but also involves or induces psychological trauma to the patients through repeated hospitalization and multiple invasive investigations if the underlying cause remains undetected. Bacteria migration, along congenital or acquired pathways from the skull or spinal dural defects, gains entrance into the central nervous system (CNS) and should be taken into consideration when children face recurrent bacterial meningitis, however, symptoms and signs of cerebrospinal fluid (CSF) rhinorrhea or otorrhea are rare in such patients. Without evidence of CSF leakage, a cranial symptom/sign or coccygeal cutaneous stigmata may suggest the approximate lesion site, diagnosis and detection remains difficult. To detect an occult dural lesion along the craniospinal axis, such as basal encephalocele, dermal sinus tract, or neurenteric cyst, a detailed clinical evaluation and the use of the modern diagnostic imaging methods is necessary. Because of the possibility of concomitant occurrence of more than one malformation, both the frontal and the lateral skull base should be carefully evaluated. Precise localization of the dural lesion is a prerequisite for successful surgical repair. In addition, the bacteria specificity could leave significant clues: Pneumoccocus or Hemophilus suggests cranial dural defects, *E. coli* or other gram negative bacilli suggests spinal dural defects, and meningococci suggest immunologic deficiency. Asplenia or immunodeficiency such as complement or immunoglobulin deficiency rarely causes recurrent meningitis without a history of frequent infection of non-CNS areas. *Salmonella* meningitis or brain abscess should not be treated incompletely or inadequately and could lead to recrudescence, relapse or recurrence of bacterial meningitis. Antibiotic (penicillin or trimethoprim-sulfamethoxazole) induced meningitis may repetitively occur on occasion. *(Chang Gung Med J 2005;28: 441-52)*

Key words: bacterial meningitis, basal encephalocele, cerebrospinal fluid leakage, immunodeficiency, recurrent meningitis, *Salmonella* meningitis

Despite the availability of modern antibiotics, bacterial meningitis is still a potentially life-threatening infection of the cranial and spinal leptomeninges.[1] The mortality rate is 10% to 25% in infants, 3% to 7% in small children, and 10% to 25% in adults.[2-4] Even if the meningitis is not fatal, seque-

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lae such as epilepsy, cranial nerve palsies, and hydrocephalus can occur. The golden rule of early diagnosis and treatment to achieve a good outcome has not yet been challenged by the new, often expensive antibiotics, or the contemporary critical care for children with bacterial meningitis.

A single episode of bacterial meningitis is often the result of blood borne bacteria. A second episode of meningitis is considered a recurrence if resulting from a different bacterial pathogen than the first, or if resulting from the same organism but occurs more than three weeks after the completion of therapy for the initial episode.[2] It is not easy to detect the underlying etiologies for patients with high risk of recurrence when the bacterial meningitis occurs for the first time unless there is a history of skull base injury or the presence of cerebrospinal fluid (CSF) leakage. However, for those with recurrent bacterial meningitis, a discharge from hospitalization is disallowed without a series of studies (examinations/tests) to detect the possible routes of migration of bacteria to the CSF space.[5] A comprehensive often exhaustive search for the mechanism of recurrent episodes must be pursued.[6] Bacteria can migrate along congenital performed pathways or acquired tissue planes to gain entrance into the subarachnoid space.[7] Another well described mechanism of recurrent meningitis is an undiagnosed immunodeficiency that can render the host defenses as inadequate barriers to potential bacterial pathogens.[8]

Bacterial meningitis due to certain specific pathogens such as *Salmonella* may relapse or recrudesce after incomplete or ineffective antibiotic treatment.[9-10] Clinically, *Salmonella* meningitis on occasion is difficult to differentiate from recurrence of bacterial meningitis. However, it usually occurs one week to ten days after cessation of the antibiotic treatment for the first episode if the appropriate antibiotic treatment lasts no longer than three weeks. Finally, there are antibiotics which could induce recurrent meningitis.[11,12]

It is speculated that bacterial meningitis may become an uncommon disease in the future. On the contrary, the relative incidence of recurrent meningitis with underlying structural or immune abnormalities may increase. The following review aims to focus on the clinical approach to children with recurrent bacterial meningitis. It is hoped that recurrence can be reduced to a minimum by detecting and treating the underlying mechanism as early as possible.

Anatomic Defects

Bacteria migration, along congenital or acquired pathways from the skull or spinal dural defects, gaining entrance into the subarachnoid space is a notable occurance for children with recurrent bacterial meningitis. Meningitis can be the sole symptom. Defects can act as portals of entry for the bacteria that are almost always present in the paranasal sinuses, gut, or skin surface, thus leading to the development of meningitis.[13] *Streptococcus pneumoniae* is found in about 80% of cases with cranial dural lesions.[14] *Staphylococci* are usually found in cases with cutaneous association, and gram negative rods found in cases with enteric association. Acquired dural lesions are usually caused by trauma or previous surgery with a relevant or remote history. Congenital lesions are usually occult and hard to diagnose even with modern imaging studies. Antibiotics can temporarily treat the symptoms of bacterial meningitis. However, without effectively eliminating the underlying cause, recurrence of meningitis is anticipated. In cases of recurrent nosocomial meningitis, a neurosurgical procedure preceded either the initial episode or a recurrent episode, and the probability of CSF leakage is about 50%.[2]

In the series of Lieb et al.,[7] no immunodeficiency was found in the 25 children suffering 2-13 episodes of bacterial meningitis. The cause of recurrent meningitis was an anatomical lesion with 13 intracranial defects including encephaloceles, skull fractures, Mondini dysplasias, neurenteric cyst, fibrous dysplasia, persistent craniopharyngeal duct, and 12 lumbosacral defects with a dermoid cyst within the lumbosacral spine. In total, 84 episodes of meningitis were treated, a pathogen was isolated in 77%. The most common pathogen was *Streptococcus pneumoniae*, followed by *Escherichia coli*, Staphylococci and others. The isolated pathogen often suggests the location of the defect. A personal history relating to possible defects was often unrewarding and in some cases the search for the anatomical lesion required repeated imaging and explorative surgery. In 24 of 25 cases, the final treatment of recurrent meningitis was surgical intervention.[7]

Cranial dural lesions (Table 1)

Dural lesions can occur as a result of trauma,

Table 1. Classification of Encephaloceles Based on the Location of the Skull Defect

I. Occipital Encephalocele
II. Encephalocele of the Cranial Vault
A. Interfrontal encephalocele
B. Anterior fontanel encephalocele
C. Interparietal encephalocele
D. Posterior fontanel encephalocele
E. Temporal encephalocele
III. Frontoethmoidal Encephalocele
A. Nasofrontal encephalocele
B. Nasoethmoidal encephalocele
C. Nasoorbital encephalocele
IV. Basal Encephalocele
A. Transethmoidal encephalocele
B. Sphenoethmoidal encephalocele
C. Transsphenoidal encephalocele
D. Frontosphenoidal / Sphenoorbital encephalocele

surgery, inflammation (osteomyelitis), tumors, malformations, increased CSF pressure, or spontaneously.[15,16] It can be difficult to decide whether an occult dural lesion is of traumatic or congenital origin. Traumatic dural lesions can remain asymptomatic for decades.[16] Moreover, patients frequently fail to recall significant minor or old injuries. When looking for a dural lesion, it is always important to evaluate both the frontal and the lateral skull base. In the region of the lateral skull base, malformations are reported to be most common in the region of the inner ear.[17]

CSF leakage, especially in a patient with meningitis, should always prompt a thorough search for an occult dural lesion.[18] However, mild CSF leakage often escapes the patient's attention or a necessary determination of the albumin-prealbumin ratio for qualitative confirmation of the presence of CSF. If the fluid drains into the nasopharynx, for example, it is scarcely noticeable. The potentially serious consequences for the patient failing to detect an occult dural lesion justify the concerted use of the modern investigational methods available today. High-resolution computed tomography, fluorescein endoscopy, cisternography, and magnetic resonance imaging can be used to diagnose occult malformations of the skull base.

Malformations of the skull base are rare. Their location and origin can be explained on the basis of embryogenesis and the various possibilities of maldevelopment. In a classification based on organogenesis, Pfeifer distinguishes between anomalies arising in the region of the forebrain (prosencephalon), the midbrain (mesencephalon), and the hindbrain (rhombencephalon).[19] Malformations of the skull base also can be classified in the context of craniofacial anomalies and clefts. Tessier describes 14 types of paramedian clefts.[20]

A new embryological approach has been formulated by Otto.[21] During embryogenesis, mesenchymal clefts with epithelial duplications occur between the branchial arches in the pharyngeal pouches at points where the ectoderm and endoderm come into direct contact with each other. The oropharyngeal membrane and the cloacal membrane are typical examples of such epithelial duplications. The failure of such mesenchymal clefts to close (inhibition malformation) leads to the development of the encephaloceles of the skull base, of which the transethmoidal type is the most commonly observed.[22,23] The reported incidence of encephaloceles is between 1:10000 and 1:100000, with 10% to 25% affecting the anterior skull base.[23,24] However, in certain areas of Southeast Asia, frontoethmoidal encephalocele have a relatively high incidence as 1:5000 live births.[25] However, the classification of encephaloceles modified from Suwanwela and Suwanwela is simple and clear-cut (Table 1).[26]

A clinical distinction can be made between manifest and occult malformations of the skull base (Table 2). In the case of manifest malformations, there are external signs of the abnormality. Protuberances, clefts, hypertelorism, facial deformities, and various types of dysfunction are prominent examples. Differential diagnosis must be ascertained for fear of malpractice. A sincipital encephalocele could be mismanaged as a hemangioma,[27] and transethmoidal encephaloceles as nasal polyps. Occult malformations have no external manifestations and are therefore only discovered when complications arise. These are most commonly recurrent meningitis and CSF rhinorrhea.

A dural lesion is assumed to be of congenital origin if there is no other satisfactory explanation, such as a history of trauma or possible iatrogenic damage, an inflammatory or neoplastic process, elevated intracranial pressure, or other relevant intraop-

Table 2. Characteristics of Manifest and Occult Malformations of the Dural Lesions

CRANIAL DURAL LESIONS
Manifest malformations
Outwardly visible (sincipital encephalocele, nasal glioma, dysmorphic face or cranium etc.)
CSF leakage (CSF rhinorrhea, CSF otorrhea, etc.)
Functionally disturbed (hearing, olfactory, or visual impairment, etc.)
Inflammatory (local pain, or heat, etc.)
Occult manifestations
Not outwardly visible (basal encephalocele)
Complications (meningitis) as first sign
SPINAL DURAL LESIONS
Manifest malformations
Outwardly visible (myelomeningocele, or other cutaneous stigmata)
CSF leakage
Functionally disturbed (sphincter, or leg impairment, etc.)
Inflammatory (local pain, or heat, etc.)
Occult manifestations
Not outwardly visible (neurenteric cyst, etc.)
Complications (meningitis) as first sign

erative findings. The concomitant occurrence of two occult malformations of the skull base is rare. Literature reflects the following: a meningocele of the anterior skull base and a defect in the stapedial footplate,[28] a meningoencephalocele of the cribriform plate and a fistula at the oval foramen, a meningocele through a cleft crista galli and a fistula at the oval foramen,[29] and the fourth, defects in the region of the cribriform plate and an inner ear malformation with a fistula through the stapedial footplate.[30,31]

Congenital or spontaneous meningoencephalocele of the medial skull base is a rare entity.[32] If not considered as a diagnostic entity, it can remain undetected or approached incorrectly, leading to unnecessary surgeries. These lesions may not present with the typical findings associated with lateral temporal bone defects such as conductive hearing loss, persistent middle ear effusion, pulsatile tinnitus, and persistent otorrhea. Pulsatile tinnitus in the lateral temporal bone encephalocele is usually caused by direct contact of the mass with the ossicular chain. Subclinical rhinorrhea may be present with medial temporal bone encephalocele, because there is a presumed communication between the medial skull base defect and the Eustachian tube.

Delayed post-traumatic erosion of the skull base was reported in three patients who presented as adults with CSF fistulae and a history of recurrent meningitis. These skull defects were associated with herniation of the subarachnoid space into the diploe of the skull base, the paranasal sinuses and the orbit. This rare complication of head injury is assumed to have occurred as the result of a dural tear at the time of trauma. Its site probably determines whether a resulting meningocele widens the intradiploic space or broaches the cranial floor.[33]

Accurate diagnosis of an occult malformation makes it possible to perform the necessary surgical repair and thereby prevents the further occurrence of potentially fatal episodes of meningitis.[19] Surgical intervention should proceed directly after controlling the infection.[23] Water-tight closure of the dural defect is the only method to effect a cure. An intracranial approach is the most suitable approach for surgical treatment. Endoscopic sinus surgery has altered the traditional approach from the nasal chamber and anterior cranial base.[34]

Spinal dural lesions (Table 2)

Cutaneous abnormalities on the midline back may represent underlying congenital malformations of the spine.[35] One such anomaly, the congenital dermal sinus, is a superficial depression or tract in the skin that is lined by stratified squamous epithelium. Its appearance can signify the presence of an abnormal connection between the skin surface and subarachnoid space and/or an occult dysraphic state. This potential communication places the child at an additional neurological risk of meningitis and recurrent meningitis. These congenital dermal sinuses are frequently associated with other cutaneous stigmata, occult dysraphic lesions, or intraspinal tumors. Although some individuals remain asymptomatic throughout adulthood, others may develop progressive dysfunction of the lower limbs and bladder due to spinal cord tethering. The insidious fashion in which such complications develop may lead to irreversible damage before any symptomatic manifestation. The risk of neurological deterioration exists at

all ages and increases with time and is frequently progressive.[36-43] The detection of such a subtle cutaneous anomaly in a child may be crucial to future neurological, urologic, and orthopedic development.

Congenital dermal sinuses can be located anywhere along the craniospinal axis. Embryologically, the lesions are thought to develop from faulty neurulation. The neural ectoderm incompletely separates from the cutaneous surface ectoderm, a term referred to as incomplete dysjunction.[44] Histologically, the sinus tract is lined by stratified squamous epithelium with surrounding dermal tissue. The majority of these lesions occur in the lumbar or lumbosacral region followed by the occipital and thoracic regions, respectively. They may extend rostrally with a considerable distance to terminate several spinal segments above the cutaneous ostium.[45] The dermal sinus tract may actually end blindly in the subcutaneous tissue or it may extend into the spinal canal, as it does in nearly one half of cases. They are infrequently associated with complex vertebral abnormalities unless other forms of occult spinal dysraphism are present.

Congenital cutaneous abnormalities are relatively common in the coccygeal region. It has been determined that two to four percents of children harbor intergluteal dorsal dermal sinuses.[46] These sinuses may become susceptible to local recurrent infection from trauma or hirsuitism. They are not related to acquire pilonidal conditions observed in adults.[47] The cause is not entirely understood. Ultrasonography may achieve diagnostic screening for patients, especially neonates or young infants, with low back cutaneous stigmata or suspicious CSF leakage.[48-50]

Neurenteric or Enterogenous cyst

Another rare etiology occasionally causing bacterial meningitis with recurrent potential is neurenteric or enterogenous cysts.[51] They result from abnormal separation of the neural tube and the endodermis during the third week of gestation, leading to the persistence of endodermal elements in the spinal canal.[52-53] Neurenteric cysts are derived from displaced endodermal tissue and are commonly encountered in the posterior mediastinum. Controversy persists about their exact embryopathogenesis, but it is well established that they result from a disruption occurring in the third week of embryogenesis and involving the complex series of interactions responsible for the formation of the notochord, neurenteric canal, endoderm, and neural tube.[53-54] These cysts may rarely occur at any level of the neuraxis from posterior clinoid to coccyx, but are most commonly found in the lower cervical and upper thoracic region and rarely in a lumbosacral location.[55] Their location may be intraspinal (extradural or intradural, and occasionally intramedullary),[56] extraspinal - most commonly in posterior mediastinum - or both,[57] entering the spinal canal through a vertebral body defect.[52] In the majority of cases an attachment to the alimentary tract is identified.[58] The cysts are generally located ventral to the spinal cord and cervicomedullary junction. The mesodermal disturbance is commonly reflected in vertebral body anomalies.[59] The cysts are lined by mucin-producing, nonciliated, simple or pseudostratified cuboidal or columnar epithelium.[58]

Wilkins et al. reviewed 119 (76 men and 43 women) patients with intraspinal neurenteric cyst.[60] The diagnosis of neurenteric cyst was established during the first decade of life in 34% of cases and in the second decade in 23% of cases. The clinical spectrum of neurenteric cyst depends on the site of the lesion and includes signs of spinal cord compression, such as local pain, radiculopathy and/or myelopathy.[61] Neonates and young children frequently present with symptoms related to an intrathoracic or intra-abdominal cyst; which rarely leads to a picture suggestive of meningitis.[62-63]

Immune Deficiency

Although people with bacterial meningitis lack adequate protective antibody against the invading pathogen, most do not have an underlying immunodeficiency. So, an evaluation for immunodeficiency is not indicated for most patients with bacterial meningitis, particularly when the disease occurs in a previously healthy individual without a history of recurrent infections before the episode of meningitis, or when risk factors for HIV infection are not present. However, levels of immunoglobulin G (IgG), immunoglobulin M (IgM), and immunoglobulin A (IgA) should be measured in children who have a history of recurrent infections, including meningitis, sepsis, or recurrent upper and lower respiratory tract infections, before an episode of bacterial meningitis.[64]

All children who have a second episode of bac-

terial meningitis should be screened for congenital immunoglobulin or complement deficiencies. Elevated immunoglobulin E (IgE) levels may be associated with some immunodeficiency (e.g., Wiskott-Aldrich syndrome), and isolated IgA deficiency may be associated with IgG-subclass deficiencies, such as IgG2 or IgG4 deficiencies. Such deficiencies have been associated with increased rates of pneumococcal and other encapsulated bacterial infections. In addition, serological testing for HIV infection should be considered for children who have bacterial meningitis if additional risk factors are present in the parents. In general, some experts recommend an immunologic evaluation if a single episode of meningitis occurs at an age that is either earlier (e.g., < six months of age) or later (e.g., three to four years of age) than is characteristic for the causative meningeal pathogen. Quantitative assessment of B cells should be performed if total levels of IgM and/or IgG are low. In addition, early component complement deficiencies, particularly C2 or C3 deficiencies; may predispose children to pneumococcal or *Haemophilus* infections, and screening can be accomplished by an assessment of total complement function (CH50). However, if suspicion is high, measurement of individual complement components and properdin proteins should be considered. Blood smear to seek Heinz bodies and abdominal ultrasound to rule out asplenia which is associated with infections with encapsulated bacterial pathogens.[65]

Records of seventeen patients who had two or more attacks of bacterial meningitis were collected from eight centers in the United Kingdom for retrospective analysis.[66] Thirteen patients had intracranial abnormality; of seven with head injury five produced CSF rhinorrhea. The first of the twenty-eight attacks seen in these occurred between a few weeks and twelve years of the head injury. Pneumococci in CSF were identified in twenty five episodes. Of six patients without a history of head injury, one had spontaneous CSF rhinorrhea and five had pathological changes of the ear. Various microorganisms were found in the CSF during the twelve attacks in the five patients. Four of the seventeen patients had primary complement deficiency (C7, C5, C4 and C3b inhibitor); ten (possibly eleven) of sixteen attacks in these cases were due to *Neisseria meningitidis*. Correction of complement deficiency is not practical at present. In some patients prophylaxis with antibiotics is the only method of preventing future attacks.[67]

Recrudescence, Relapse or Others Mimicking Recurrence

Antibiotic therapy of bacterial meningitis in children may be complicated by reappearance of bacteria in CSF during therapy (recrudescence) or within three weeks after antibiotics have been stopped (relapse). Recrudescence and relapse occurred mainly in children less than two years of age and comprised less than one percent of all patients in a series of childhood bacterial meningitis.[9] Host immunity is a problem. However, incorrect use of antibiotics, either poor blood-brain-barrier penetration or inadequate dosage or treatment length, is another problem. Routine CSF examination at the end of adequate antibiotic therapy is not necessary or useful when the patient has exhibited a satisfactory clinical response, since relapse did not become manifest until three or more days after discontinuation of antibiotics. Relapse after adequate therapy of bacterial meningitis was usually ascribed to persistence of infection in meningeal or parameningeal foci whereas recrudescence was usually caused by ineffective therapy. *Salmonella* meningitis in young children is typical of the latter to be recrudescent.[10,68]

Although *Salmonella* strains only account for one percent or less of the confirmed cases of bacterial meningitis in neonates and infants in developed countries,[69] we have experienced up to 20% at our hospital in northern Taiwan.[10] The possibility of *Salmonella* infection should be always kept in mind whenever Gram-negative rods are seen in CSF. Overall, antibiotics for treating *Salmonella* meningitis in children have not been as successful as those used to treat *E. coli* meningitis.[70] Antibiotics used previously, either alone or in various combinations, have included chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole. Some isolates are now resistant to one or more of these agents and reports suggest that treatment with ampicillin and/or chloramphenicol has been associated with a mortality rate of about 30%.[71,72] The American Academy of Pediatrics now recommends that treatment for *Salmonella* meningitis with cefotaxime or ceftriaxone should continue for four weeks or more,[73] although relapses following cefotaxime therapy have been reported even with the recommended four

weeks of treatment.[74] Meningitis caused by *Salmonella* spp. resistant to cephalosporins is uncommon.[75] So far, there is insufficient experience with imipenem and meropenem to judge whether they provide any therapeutic advantage.[75] As an alternative, Price et al. suggest that consideration should be given to a combination of ciprofloxacin and ceftriaxone or cefotaxime.[76] Data on the optimal duration of therapeutic regimens are lacking, but we would suggest that both agents should be administered for a minimum of three weeks.

After an apparent satisfactory clinical response to antibiotics, including the CSF returning to its normal appearance in cell counts and sugar contents, physicians and parents should be educated in the need for symptomatic self-diagnostic vigilance because of the possibility of relapse.[10,77] This may occur days or even weeks after apparent successful antibiotic treatment and although it is not always easy to detect in the early stages, progression may be rapid.[69] As well as involving the CNS, relapse may be septicemic. Choice of antibiotics and dose for treatment of relapse should be based on the patient's presenting problem, together with the sensitivity results from the new isolate. Although not uncommon, the new sensitivities will be the same as those originally detected and the relapse probably reflects the intracellular localization of the organism, together with inadequate antibiotic penetration into the CNS macrophages or other parts of the reticuloendothelial or biliary-intestinal systems. Length of antibiotic treatment following a relapse should exceed the original treatment period by a considerable margin.[10,76]

Penicillin or trimethoprim-sulfamethoxazole administration has been reported on occasions to mimick bacterial meningitis repetitively in the same candidate with CSF pleocytosis and hypoglycorrachia as bacterial meningitis.[11,12] Recurrent meningitis can occur in patients who suffer ineffective management of brain abscess too.

Diagnostic Investigations

In the study by Lieb et al.,[7] 52% of children with recurrent bacterial meningitis had cranial dural etiologies, while in the study by Drummond et al. there were 33%.[5] Physicians should first consider that a chronic ear infection or paranasal sinusitis might be the underlying cause. The search for CSF leakage in a young child with recurrent meningitis should start with a thorough and detailed record of its history and a complete physical examination. A history of skull trauma is often neglected because of the considerable duration of time between a head injury and meningitis secondary to CSF leakage.[78] Other aspects of the history include any previous surgical procedures performed on the ear, sinus, skull base or spleen. When recurrent meningitis is associated with episodes of otitis media, the history and physical examination should be directed towards looking for an otogenic source. An otoscopic examination and audiological evaluation are performed to look for the possible otologic source of recurrent meningitis. When sensorineural hearing loss is identified in a post-meningitis child, both infectious or pre-existing congenital factors as possible etiologies of the hearing loss must be considered. In Fartnum's review of the literature, he found that the incidence of sensorineural hearing loss after an episode of meningitis ranged from 6.6 to 11.7%.[79] A child with recurrent meningitis and congenital sensorineural hearing loss should be strongly suspected of having a translabyrinthine CSF fistula.

CSF leaks are often intermittent and may not be easily identified.[80] CSF rhinorrhea is particularly difficult to diagnose in young children and infants, one reason being the patient's inability to provide an adequate history. Quiney et al.[29] gave five reasons why otogenic CSF rhinorrhea is frequently misdiagnosed in children:

1. CSF rhinorrhea can be indistinguishable from nasal discharge.

2. A middle ear effusion is rare because CSF usually drains down the Eustachian tube. If the child does present with a middle ear effusion, it may be mistaken and treated as otitis media.

3. CSF may run down the Eustachian tube and be swallowed rather than present as a nasal discharge.

4. Children with recurrent meningitis are often investigated by axial computed tomographic (CT) scanning to look for intracranial abnormalities or anterior cranial fossa defects. If the cuts are not administered low enough or if the bone window settings are incorrect, the fine details of the vestibulecochlear system will be missed.

5. Unilateral deafness may be difficult to diagnose in a young child with no otologic symptoms.

If CSF leakage is suspected, the positive identification of the leakage can take different forms. Traditional testing of nasal discharge or middle ear fluid for its glucose content is unreliable and should be replaced by testing for B2-transferrin,[81] or β-trace protein (prostaglandin D synthase).[82]

A contrast enhanced CT scan of the head should be performed with thin section (2mm) tomography of the temporal bone and coronal images of the anterior skull base.[83,84] Although the CT scan may demonstrate a bony defect and suggest the site of the CSF leakage, the additional technique of cisternography may be needed to positively identify the leak. CT cisternography is currently the most reliable technique for the accurate localization of CSF leakage and is replacing radioisotope cisternography as the preferred method in many centers.[85,86] High-resolution magnetic resonance (MR) scans were very helpful for differential diagnosis. Three-millimeter axial and coronal T1-weighted and fast spin-echo T2-weighted images showed predominantly CSF material within the meningoencepholaceles, as well as some brain intensity tissue. MR imaging is a sensitive and accurate technique for detection of CSF leakage even in patients who are not actively suffering leakage at the time of evaluation.[87] MR imaging is also non-invasive, offers excellent anatomical detail and has no radiation risk. A study by Eljamel et al. has demonstrated the benefits of T2 – weighted MR cisternography in identifying the site of inactive CSF fistulas which are not identified by CT cisternography.[88] Also, fluorescein injected into the CSF can be useful for both preoperative and intraoperative identification of a CSF leakage, although rare adverse reactions to the dye have been described.[89] How far does the physician need to go to try identifying CSF leakage or an anatomical abnormality when a child presents with recurrent meningitis? In Lieb's review of 25 patients with recurrent meningitis, an anatomical lesion was identified in all 25 patients. They stated that exhaustive diagnostic procedures be carried out in all cases of recurrent meningitis.[7] Parisier et al. even go as far as recommending surgical explorations of any radiologically abnormal non-hearing ear.[90]

Although it is difficult to make recommendations, the current evidence suggests that the initial investigation of recurrent bacterial meningitis should include a contrast enhanced CT scan of the temporal bones and the anterior skull base including the paranasal sinuses. Other more invasive studies, such as CT, MR, or radioisotope cisternography, may be required to confirm and locate a cranial dural defect. At the same time, especially when there is skin abnormality on the back or the pathogen of meningitis is always gram-negative bacilli or staphylococci, a spinal dural defect must be sought. Ultrasound may be affordable for young infants. Otherwise, a further MR study of spine must be undertaken. If all the imaging studies are negative, immunological studies should be performed, including a complete blood count with erythrocyte morphology, total immunoglobulin levels, immunoglobulin G subclasses and total hemolytic complement levels. If the imaging studies are abnormal but no CSF leakage can be demonstrated, immunological studies should be considered before resorting to surgical exploration. Splenic function can be examined using a liver/spleen radionucleotide scan if there is a history or blood test suggestive of hyposplenia.

The sequence of investigations regarding recurrent meningitis will be dictated by what is found during the initial history taking and physical examination. If no etiology is identified when recurrent meningitis is diagnosed in the pediatric patient the following protocol is proposed:

1. An audiological evaluation - audiogram or brainstem auditory evoked potential.
2. A contrast enhanced CT scan of the head including coronal images of the sinuses and fine cuts through the temporal bone.
3. Spinal ultrasound or MR imaging if otherwise indicated.
4. Immunological studies, including a complete blood count, total immunoglobulin levels, immunoglobulin G subclasses and total hemolytic complement levels.

Conclusion

Recurrent meningitis in children is not only potentially life threatening, but often involves the child in repeated hospitalization, multiple and invasive investigations. Symptoms and signs of CSF leakage are rare in these patients. Diagnosis and detection without a CSF rhinorrhea or otorrhea, a cranial symptom/sign or a coccygeal cutaneous stigmata which may suggest the lesion site, remains difficult. Alternatively, the bacteria specificity often

suggests a possible lesion site. The combined use of all the modern clinical and diagnostic imaging methods available is necessary for detection of an occult dural lesion. Precise localization of the dural lesion is a prerequisite for surgical repair. Immune deficiency is rare without history of frequent infection. Salmonella meningitis or brain abscess should not receive incomplete or insufficient treatment. And finally, antibiotic induced meningitis may on occasion appear as a repetitive occurrence.

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兒童復發細菌性腦膜炎的診斷方針

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兒童復發性細菌性腦膜炎不僅潛藏致命的危機，病童因需一再住院接受許多侵襲性檢查，以便找到導致腦膜炎復發的病因而產生心理挫傷，也不容忽視。正常的中樞神經系統爲周密的骨骼及腦膜包圍保護著，先天或後天（外傷、手術）的硬腦膜缺陷使細菌易於一再侵入，因而兒童復發細菌性腦膜炎時確定有無硬腦膜缺陷的存在與位置爲最首要；腦脊髓液從鼻、耳滲漏出的機會並不大，倒是顏面或背部的異樣有時暗示著硬腦膜缺陷的可能位置。爲了找得到潛在的病灶，常需合併用到所有現代化影像檢查。同時施以正確的外科硬腦膜縫合術治療到滴水不漏，才足以避免腦膜炎又再復發。顱底的腦膨出 (basal encephalocele)、脊髓或後腦窩通到皮膚或消化道的瘺管 (sinus tract 或 neurenteric cyst) 等雖都罕見，但在某些東南亞地區高達每五千名活產兒就有一例顱底腦膨出；另外常合併扯髓 (tethered cord) 的脊髓病變，用前瞻性的外科治療可避免將來產生進行性的下肢和排尿問題。沒有解剖構造上的病灶時，免疫缺陷是接下來診斷努力的方向，這類病人平時就經常一再感染，除了免疫球蛋白或補體不足之外，無脾症 (asplenia) 也是腦膜炎復發的病因之一。至於像沙門氏桿菌引起的腦膜炎，常常因抗生素治療不足三週以上，而於停藥不久就出現類似復發的現象，臨床醫師不能不謹慎。(長庚醫誌 2005;28:441-52)

關鍵字：細菌性腦膜炎，顱底腦膨出，腦脊髓液滲漏，免疫缺陷，復發性腦膜炎，沙門氏菌腦膜炎。

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