Meningitis and encephalitis in infants and children

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ABSTRACT

مازال التهاب السحايا والدماغ من الأمراض الخطيرة التي تصيب الأطفال وبمعدل وفيات يصل إلى 25% وذلك بالرغم من توفر العلاجات الحديثة. يعاني كثير من المصابين من مضاعفات متعددة وطويلة الأجل ومنها الصرع، والصعوبات الذهنية والسلوكية. وتظل القاعدة الذهبية بالتشخيص والعلاج السريع أهم من توفير العلاجات الحديثة أو العلاج بالعناية المركزة. نقدم في هذا المقال مراجعة حديثة لالتهابات السحايا والدماغ لدى الرضع والأطفال. ومن المهم أن نشير إلى أهمية التطعيمات في تقليل نسبة الإصابة بهذه الالتهابات الخطيرة، ولكنها مازالت من المشاكل التي تواجه الدول النامية التي تنخفض فيها نسب التطعيم. تشمل الالتهابات الفيروسية كلاً من الفيروسات المعوية، وفيروس الهربس البسيط، والفيروسات المنقولة بالمفصليات، ومع ذلك فإنه قد يصعب الكشف عن الالتهابات الفيروسية وذلك بمعدل يتعدى 70% من الحالات. وبالمقابل فإنه يسهل تحديد الالتهابات البكتيرية إلا إذا تناول المريض سابقاً المضادات الحيوية عن طريق الفم، مع العلم أن هذه الالتهابات تختلف حسب عمر المصاب. وتصيب الالتهابات الفطرية الغير منتشرة المرضى المصابين بنقص المناعة.

Despite the availability of modern therapies, meningitis and encephalitis remain potentially life-threatening infections in children with mortality rates reaching up to 25%. Treated patients are at a high risk of long term sequelae including epilepsy, learning, and behavioral disorders. 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 contemporary critical care. In this article, an updated overview of meningitis and encephalitis in infants and children is presented. It is important to note that routine childhood immunization has significantly decreased the number of serious infections. However, meningitis and encephalitis remain problematic particularly in developing countries where immunization rates are suboptimal. The most common viral etiologies include enteroviruses, herpes simplex virus, and arboviruses. However, the causative virus may not be identified in up to 70% of cases. This is not the case for bacterial infections unless the patient had received prior oral antibiotics. The causative bacterial organisms vary with age, and the less common fungal infections occur mainly in immune compromised patients.

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Infections of the meninges (meningitis) and the brain (encephalitis) need to be identified and managed promptly in order to prevent associated morbidity and mortality.[1] Despite the availability of modern antibiotics, bacterial meningitis is still a potentially life threatening infection. The mortality rate is 10-25% in infants, 3-7% in young children, and 10-25% in adults.[2-4] Even if the meningitis is not fatal, sequelae such as epilepsy, cranial nerve palsies, hydrocephalus, learning, and behavioral disorders 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 contemporary critical care. Symptoms and signs suggestive of raised intracranial pressure (**Table 1**) are frequently the initial features of meningitis caused by viral or bacterial infections.[5] Encephalitis is more frequently caused by viral infections with features that include seizures, personality change, decreased consciousness, and focal neurological manifestations. As the infection progress, mixed features are frequently encountered (meningo-encephalitis). In this article, an updated overview of meningitis and encephalitis in infants and children is presented.

Etiology. Routine childhood immunization has significantly decreased the number of serious infections. However, viral infections remain more common than bacterial infections. Both are more problematic in developing countries where immunization rates are suboptimal.[6] The most common viruses that cause meningitis and encephalitis are listed in **Table 2** and included enteroviruses, herpes simplex virus, and

arboviruses. In clinical practice, the causative virus cannot be identified in up to 70% of cases. This is not the case for bacterial infections unless the patient received prior oral antibiotic therapy. The causative bacterial organisms vary with age as shown in **Table 2**. Other infections causing meningoencephalitis in children, including fungal, are less common in immune competent patients.

Viral infections. Aseptic meningitis. Viral meningitis is a benign, self-limited disease from which most children recover completely.[7] The term "aseptic" implies the presence of meningismus and CSF leukocytosis without a documented bacterial or fungal infection.[8] Enteroviruses are responsible for most cases, however, non-viral causes could be considered including Lyme disease, Kawasaki disease, leukemia, systemic lupus erythematosus, migraine, and drugs. In viral infections, the onset of symptoms is abrupt and characterized by fever, headache, and stiff neck, except in infants who do not have meningismus because of their open fontanels and sutures.[9] Irritability, lethargy, and vomiting are common. The CSF contains 10-200 leukocytes/mm^3, which are primarily lymphocytic. The protein concentration ranges between 50-100 mg/dL with normal glucose. Bacterial meningitis cannot be ruled out at the onset; therefore, antibiotic therapy is indicated routinely until the CSF culture is negative. This is especially true for children who received prior oral antibiotics. Treatment for possible herpes encephalitis with acyclovir is also indicated at the onset until the diagnosis is excluded (see next section). Otherwise, treatment of viral aseptic meningitis is symptomatic.[7] Bed rest, quiet environment, and mild analgesics provide symptomatic relief. The acute illness usually lasts less than one week, but malaise, and headache may continue for several weeks.

Table 1 - Important symptoms and signs (red flags) suggestive of raised intracranial pressure.[5]

Symptoms
1. Headache progressive in severity or frequency
2. No relief with regular analgesics
3. Sleep-related or early morning headache
4. Worsened by cough, micturition, or defecation
5. Persistent vomiting without nausea
6. Personality change
7. Other neurological symptoms (for example, seizures, double vision, weakness)
Signs
1. Bulging fontanel
2. Separated sutures
3. Lethargy
4. Neck stiffness
5. Papilledema
6. Focal neurological signs (for example, motor, sensory, cerebellar)

Encephalitis. Herpes Simplex virus (HSV) is the most serious treatable etiology of encephalitis.[10] Other causative viruses are listed in **Table 2** and are less common. The HSV encephalitis accounts for 10-20% of cases with an estimated annual incidence of 2.3 cases per million population.[11] The HSV-1 (orofacial) is the causative agent of acute encephalitis (usually focal) after the neonatal period and HSV-2 (genital) is the causative agent of encephalitis (usually diffuse) in the newborn.

In HSV-1, the initial orofacial infection may be asymptomatic. The virus replicates in the skin, infecting nerve fiber endings with retrograde neuronal infection reaching the olfactory or trigeminal ganglia, where the virus enters a latent stage. Reactivation occurs during times of stress, fever, or acute illness. The reactivated virus may spread proximally to the brain, causing focal encephalitis predominantly affecting the temporal lobe (coming from the trigeminal ganglia) or the inferior frontal lobe (coming from the olfactory ganglia). An immunocompromised state results in frequent reactivation and a more severe widespread infection. Clinically, the patient develops acute symptoms including fever, headache, lethargy, behavioral changes, nausea, and vomiting. Most children (80%) develop focal neurological signs including, hemiparesis, cranial nerve deficits, visual field loss, aphasia, and seizures.

Table 2 - Common causes of meningitis and encephalitis in children.

Infection	Organisms
Viral	Enteroviruses Herpes simplex virus Myxoviruses (influenza, measles) Arboviruses Retroviruses (HIV) Rhabdoviruses (rabies)
Bacterial	
Newborn (early onset)	*Escherichia coli* *Group B streptococcus*
Newborn (late onset)	*Escherichia coli* *Group B streptococcus* Enterococci Gram negative enteric bacilli (*Pseudomonas* and *Klebsiella*) *Listeria monocytogenes*
Infants	*Streptococcus pneumonia* *Neisseria meningitidis* *Haemophilus influenzae*
School age	*Streptococcus pneumoniae* *Neisseria meningitidis* *Mycobacterium tuberculosis*
Fungal	Candida *Cryptococcus neoformans* Dimorphic forms *Blastomyces dermatitidis* *Coccidioides immitis* *Histoplasma capsulatum* Aspergillus

In HSV-2 infection, the picture is more of a diffuse meningoencephalitis. The neonate acquires such a primary infection from the mother's genital tract. The initial clinical features are similar to those of aseptic meningitis caused by other viruses. A CSF examination reveals pleocytosis with cell count within the 100s (up to 1000/mm^3). Up to 500 red blood cells/mm^3 may be present. The CSF protein concentration is usually high (80-100 mg/dL) with normal glucose. The identification of the organism in the CSF by polymerase chain reaction (PCR) has eliminated the need for brain biopsy to establish the diagnosis. The EEG demonstrates characteristic periodic lateralizing epileptiform discharges as the infection progress. However, MRI is a more sensitive early indicator of herpes encephalitis showing increased signal intensity involving the cortex and white matter in the temporal or inferior frontal lobes.

Intravenous acyclovir treatment for both HSV-1 and HSV-2 infections is indicated for 2-3 weeks. Early treatment decreases the mortality rate from 70% in untreated patients to 30%.[10,11] The highest mortality rate is in patients already in coma at treatment onset. Long-term neurological complications are common and function returns to normal in only 40% of patients.

Bacterial infections. Neonatal meningitis. Meningitis occurs in approximately 1:2000 term newborns, and accounts for 4% of all neonatal deaths. It is a consequence of septicemia, and maternal infection is the main risk factor. Early-onset (first 5 days) and late-onset (after 5 days) patterns of meningitis have been identified. In early-onset neonatal meningitis, acquisition of infection occurs at the time of delivery, and the responsible organisms are usually *Escherichia coli (E. coli)* or *Group B streptococcus* (**Table 2**). The newborn becomes symptomatic during the first week, and the mortality rate is 20-50%. In late-onset meningitis, acquisition of infection is postnatal, and the symptoms usually begin after the first week of life. Newborns requiring intensive care are specifically at risk of late-onset meningitis because of multiple instrumentations. Other organisms may be responsible including enterococci, gram-negative enteric bacilli, and *Listeria monocytogenes* (**Table 2**). The mortality rate is 10-20%. Clinical features of both infection patterns include fever, hypothermia, jaundice, hepatomegaly, lethargy, irritability, feeding difficulties, seizures, respiratory distress, and subsequent apnea and shock. Bulging fontanels occurs in only 25% of neonates. The diagnosis should be confirmed by examination of the CSF. However, even in the absence of infection, the CSF of febrile newborns averages 11 leukocytes/mm^3 (range 0-20), of which less than 6% are polymorphonuclear leukocytes. The protein concentration range is 40-130 mg/dL, and the glucose concentration range is 36-56 mg/dL. In newborns with meningitis, the leukocyte count is usually in the thousands, and the protein concentration is high. A Gram-stained smear of the CSF permits identification of an organism in up to 50% of cases. Rapid detection of bacterial antigens by immunoelectrophoresis, latex agglutination, and radioimmunoassays are helpful in the diagnosis of several bacteria. The choice of initial antibiotic therapy includes ampicillin and an aminoglycoside. An alternative regimen is ampicillin and cefotaxime. Identification of a specific organism leads to a more specific therapy. The duration of treatment for neonatal meningitis is at least 2 weeks beyond the time the CSF becomes sterile. A CSF culture should be repeated after discontinuing antibiotic therapy. A positive culture indicates the need for a second course of therapy. Permanent neurological complications occur in 30-50% of survivors and include hydrocephalus, cerebral palsy, epilepsy, mental retardation, and deafness. The type of infecting organism, and the gestational age are the main variables that determine mortality. Mortality rates are 20-30% and are highest for gram-negative infections.

Meningitis in infants and young children. For children 6 weeks to 3 months old, *Group B streptococcus* remains a leading cause of meningitis, and *E. coli* is less common. Important organisms after 3 months of age include *Streptococcus pneumoniae (S. pneumoniae)*, *Neisseria meningitidis (N. meningitidis),* and *Haemophilus influenzae (H. influenzae)* (**Table 2**). However, *H. influenzae* is becoming less common in many countries due to routine immunization.[12] The onset of meningitis may be insidious or fulminating.[13] Typical clinical features include fever, irritability, headache, vomiting, and lethargy. Seizures occur in around 30% of children. Examination reveals a sick and irritable child who resists being touched or moved.[14] A bulging fontanel is a feature in young infants; however, papilledema is rarely seen.[9] Petechial or hemorrhagic rash is seen in most children with meningococcemia.[13] Meningeal irritation causes neck stiffness, characterized by limited mobility, and pain on attempted flexion of the head.[15] Focal neurological signs are unusual except in tuberculous meningitis or in complicated cases (for example, abscess). Initial investigations include complete blood count showing leukocytosis with increased immature granulocytes. A CSF examination is essential for the diagnosis and should be performed as quickly as possible when meningitis is suspected.[16] Routine neuroimaging before lumbar puncture can result in significant diagnostic delays and therefore should be discouraged. Generalized increased intracranial pressure is always part of acute bacterial meningitis and is not a contraindication to lumbar puncture. The characteristic CSF findings include an increased pressure, cloudy appearance,

polymorphonuclear leukocytosis (thousands), decreased glucose (<50% of plasma), increased protein, positive gram stain, and culture. The CSF abnormalities may vary according to the type of organism, the timing of the lumbar puncture, the previous use of antibiotics, and the immunocompetence of the host. Cultures of the blood, urine, and nasopharynx are also indicated. The diagnosis of the syndrome of inappropriate antidiuretic hormone secretion requires measurement of serum electrolytes and requires careful fluid management.[17] Every child at risk of tuberculous meningitis requires a tuberculin skin test.[18] Antibiotic therapy should be given immediately and should not be delayed until the CSF results are obtained. Vancomycin and a third-generation cephalosporin are recommended initially. The final choice awaits the results of culture and antibiotic sensitivity. The response to treatment and outcome depends on the infecting organism and the speed of initiating therapy. A rapid decline of neurological function is indicative of the severity of cerebral edema and cerebral vasculitis. Peripheral vascular collapse can result from brainstem herniation, endotoxic shock, or adrenal failure. Up to 10% of the survivors develop sensory neural hearing loss. The incidence of hearing loss is highest with *S. pneumoniae* infection (30%). Identification of hearing loss and early rehabilitation will lessen the long-term educational and social difficulties these children may experience.[19] Some children (4%) have other long term neurological deficits.[20]

Meningitis in school-age children. *Streptococcus pneumoniae* and *N. meningitidis* account for most cases of bacterial meningitis in previously healthy school-age children, whereas *Mycobacterium tuberculosis (M. tuberculosis)* is a leading cause of meningitis in economically deprived populations (**Table 2**). The symptoms do not differ substantially from those encountered in preschool children. Predisposing conditions include otitis media, complement deficiency, sickle cell disease, asplenia, and chronic illnesses.[21] Patients at high risk require immunization with pneumococcal and meningococcal vaccines. Vancomycin and a third-generation cephalosporin are usually recommended for treatment. Penicillin G and ampicillin are equally effective in treating penicillin-sensitive strains of *S. pneumoniae*. A 2-day course of oral rifampin is prescribed for all household contacts. Up to 8% of children treated for bacterial meningitis develop major neurological deficits (for example, mental retardation, seizures, hydrocephalus, cerebral palsy, blindness, hearing loss). Learning difficulties are more commonly encountered in these patients (up to 18%) as they grow older.

Recurrent bacterial meningitis. Recurrence usually is caused by a different bacterial pathogen; however, infection by the same organism is considered a recurrence if it occurs more than 3 weeks after the completion of initial therapy.[22] Patients at risk of recurrence include those with a history of skull base injury or CSF leak. Other causes include congenital tracts, and immunodeficiency.[22] Bacteria can migrate into the subarachnoid space along congenital or acquired pathways from the skull or spinal dural defects. Meningitis can be the sole symptom and is caused by bacteria normally present in the paranasal sinuses, gut, or skin surface.[23] *Streptococcus pneumoniae* is common with cranial dural lesions, while staphylococci are found in cases with cutaneous association, and gram negative rods are found in cases with enteric association.[24] Examples of congenital anatomical defects include encephaloceles, skull fractures, neurenteric cyst, fibrous dysplasia, persistent craniopharyngeal duct, and lumbosacral defects. Dural lesions can also be acquired following trauma, surgery, inflammation (osteomyelitis), tumors, or increased CSF pressure.[25] High-resolution CT, fluorescein endoscopy, cisternography, and MRI can be all used to diagnose these rare causes of recurrent meningitis and guide the provision of the necessary surgical repair. If all the imaging studies are negative, immunological studies should be performed to exclude an underlying immune deficiency syndrome.

Tuberculous meningitis. Worldwide, tuberculosis (TB) remains a leading cause of morbidity and death in children.[18] It occurs with a higher frequency in developing countries and where sanitation is poor or with overcrowding. However, tuberculosis accounts for only 5% of bacterial meningitis in developed countries. The peak incidence of tuberculous meningitis is between 6 months and 2 years of age. Infection follows inhalation of the organism from infected contacts. Within 6 months, pulmonary tuberculosis disseminates to other organs, including the brain. The first symptoms tend to be more insidious than with other bacterial meningitides, however, a fulminant course is occasionally seen. Tuberculous meningitis, in contrast to fungal meningitis, is not a cause of chronic meningitis. If not treated, a child with TB meningitis dies within a few weeks. Most often, fever develops first, and the child becomes listless, irritable with vomiting and abdominal pain. Headache and vomiting become increasingly frequent and severe. Signs of meningismus develop during the second week after onset of fever. Cerebral infarction occurs in one third of affected children. Seizures are common, and the consciousness level declines progressively with focal neurological deficits including, cranial neuropathies, and hemiparesis. The diagnosis should be considered in any child with a household contact. General use of tuberculin skin testing in children at risk is crucial to

early detection. The peripheral white blood cell count generally is elevated with associated hyponatremia and hypochloremia as a result of inappropriate antidiuretic hormone secretion. The CSF is usually cloudy with high leukocyte count, predominantly lymphocytic. The CSF glucose declines, and the protein increases steadily throughout the illness. Smears of CSF stained by the acid-fast technique generally show the bacillus. Recovery of the organism from the CSF is not always successful, even when guinea pig inoculation is used. Newer diagnostic tests include PCR, enzyme-linked immunosorbent assay, and radioimmunoassay tests for antimycobacterial antigens with reported sensitivities reaching 75%. Early treatment enhances the prognosis for survival and neurological recovery. Isoniazid, streptomycin, rifampin, and pyrazinamide are recommended for 2 months. Isoniazid and rifampin should be continued for an additional 10 months. Corticosteroids can be used initially to reduce inflammation and cerebral edema. Communicating hydrocephalus is a common complication because of impaired CSF absorption. Complete neurological recovery is unlikely when the child becomes comatose with mortality rates reaching 20%, even with early treatment.

Fungal infections. Fungal infections of the CNS may cause acute, subacute, or chronic meningitis, in addition to abscesses and granulomas.[26] Candida and Cryptococcus infections are the most common, followed by Coccidioides, Aspergillus, and Zygomycetes (**Table 2**). Candida is a common inhabitant of the mouth and intestinal tract.[27] Ordinarily it causes no symptoms; however, Candida can multiply and become an important pathogen in children with immunosuppression, prolonged antibiotic use, debilitating diseases, transplant recipients, and critically ill children undergoing treatment with long-term vascular catheters. Candidal meningitis is extremely uncommon in healthy non-hospitalized children. Candida reaches the brain by vascular dissemination and the brain is involved less often than other organs. Fever, lethargy, and vomiting are the prominent features. Hepatosplenomegaly and arthritis may be present. As the infection progress, meningismus, papilledema, and seizures occur leading to a decreased level of consciousness. The organism can be isolated from the CSF or blood. The CSF shows a predominantly neutrophilic response with increased protein and mild decrease of the glucose concentration. Children with a candidal abscess rather than meningitis may have near-normal CSF results. The CT reveals a mass lesion resembling a pyogenic abscess or tumor. Indwelling vascular catheters should be removed, and the patient treated with amphotericin B and flucytosine for 6-12 weeks.

In conclusion, despite the availability of modern therapies, meningitis and encephalitis remain potentially life-threatening infections with significant morbidity. Routine childhood immunization has significantly decreased the number of serious infections. However, this remains problematic in developing countries where immunization rates are suboptimal. The most common viruses include enteroviruses, herpes simplex virus, and arboviruses. The causative bacterial organisms vary with age and fungal infections are less common in immune competent patients. The CSF examination is essential for the diagnosis and should be performed as quickly as possible. Routine neuroimaging before lumbar puncture can result in significant diagnostic delays and therefore should be discouraged. The CSF abnormalities may vary according to the type of organism, the timing of the lumbar puncture, the previous use of antibiotics, and the immunocompetence of the host. Every child at risk of tuberculous meningitis requires a tuberculin skin test. Antibiotic therapy should be given immediately and should not be delayed until the CSF results are obtained. The final choice awaits the results of culture and antibiotic sensitivity. The response to treatment and outcome depends on the infecting organism and the speed of initiating therapy. Major neurological deficits develop in 8% of children and up to 18% may have future learning difficulties.

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Related topics

Al-Khashan HI, Selim MA, Mishriky AM, Binsaeed AA. Meningitis and seasonal influenza vaccination coverage among military personnel in central Saudi Arabia. ***Saudi Med J*** 2011; 32: 159-165.

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