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Chapter V

Complications and Long-Term Prognosis of Bacterial Meningitis

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Abstract

Despite advances in medical care, improvement of antimicrobial and anti-inflammatory therapy and worldwide immunization programs, bacterial meningitis is still responsible for substantial morbidity and mortality in both developed and developing countries. A worldwide reported mortality rate from bacterial meningitis continues to be high, ranging between 2% and 30% and 20% of survivors develop neurological sequelae. During the last decades the disease epidemiology has changed dramatically in the countries that implemented the conjugate vaccines against the most common meningeal pathogens. Also in developing countries, gradual changes have been observed in the epidemiology of bacterial meningitis that are unrelated to the introduction of new vaccines, but are partly due to the improvement of living conditions. Numerous studies have shown that the risk of death or developing complications from bacterial meningitis is related to the age and

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underlying condition of the patient, the causative pathogen, the severity and duration of illness at the time of presentation, and, occasionally, delays in the initiation of antibiotic therapy. Common neurological complications of bacterial meningitis include impaired mental status, cerebral edema and increased intracranial pressure, seizures, subdural collections (subdural effusion, subdural hematoma or empyema), cerebritis and cerebral abscess, hydrocephalus, focal neurological deficits (hearing impairment, cranial nerve palsies, hemiparesis or quadriparesis), cerebrovascular abnormalities, ventriculitis, neuropsychological impairment and developmental disability, hypothalamic dysfunction etc.

The most frequent early neurological complications of bacterial meningitis in children are subdural effusions, recurrent seizures, and hydrocephalus. A major cause of sequelae of bacterial meningitis is intracranial complications arising during the acute phase of the disease. The most frequent long-term sequelae of bacterial meningitis in children are neuropsychological impairment ranging from learning and behavioral disorders to deafness, seizures, and motor deficits. Although many neurological complications are severe, others, such as hearing loss, may be subtle or inapparent during the early phases of infection. Age prior to 12 months was found to be a risk factor for both early neurological complications and long-term sequelae of bacterial meningitis in children.The highest risk for acute neurological complications occurred in infants and also in this age group was observed the highest incidence of long-term sequelae. The major neurologic complications of bacterial meningitis in adults include cerebrovascular involvement, brain swelling, cerebral abscess, hydrocephalus and focal neurological deficits. Several studies reported cerebrovascular complications to be the most frequent complications of bacterial meningitis in adults and prognostic factors of the disease. A decreased level of consciousness, especially coma has been identified as important risk factors associated with poor outcome of bacterial meningitis in both children and adults. From long follow up, patients with hydrocephalus had the most unfavorable outcome. A majority of childhood bacterial meningitis survivors with long-term sequelae that are documented in the literature had academic and behavioral limitations

Introduction

Bacterial meningitis is a severe infection responsible for high mortality and disabling sequelae. Before the advent of antimicrobial agents, bacterial meningitis was almost exclusively a fatal disease, with a case fatality rate of 95% to 100% for patients with pneumococcal meningitis, 90% for those with

Haemophilus influenzae meningitis, and 70% to 90% for those with meningococcal meningitis [1]. But even treated on time, bacterial meningitis is often associated with adverse outcome many often in developing countries where the burden of this disease is greater. The 3 most common etiologic agents of bacterial meningitis are *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae*, and *Neisseria meningitidis*, which account for 90% of reported cases of acute bacterial meningitis in infants and children >4 weeks of age [2, 3 , 4, 5, 6, 7, 8].

During the last decades the disease epidemiology has changed dramatically in the countries that implemented the conjugate vaccines against the most common meningeal pathogens.The widespread use of effective protein-polysaccharide conjugate vaccines caused a dramatic decline in the incidence of *H. influenzae* type B meningitis in children [3, 5, 9]. Implementation of pneumococcal and meningococcal vaccines and universal screening of pregnant women for group B streptococcus (GBS) have further changed the epidemiology of bacterial meningitis [4].

Rates of bacterial meningitis decreased most sharply among children, causing the median age at diagnosis of bacterial meningitis to increase [10]. Although vaccination with a pneumococcal conjugate vaccine is producing herd immunity among adults, the age distribution of meningitis has now shifted to older age groups [11, 12].

During the last decade, gradual changes have been observed in the epidemiology of bacterial meningitis even in developing countries that are unrelated to the introduction of new vaccines, but are partly due to the improvement of living conditions [13].

Despite advances in medical care, improvement of antimicrobial and anti-inflammatory therapy and worldwide immunization programs, bacterial meningitis is still responsible for substantial morbidity and mortality in both developed [2,14 - 22] and developing countries [23 - 28]. Bacterial meningitis is now among the top 10 infectious causes of death worldwide [29]. A worldwide reported mortality rate from bacterial meningitis continue to be high, ranging between 2% and 30% [2, 3, 30 - 38] and 20% of survivors develop neurological sequelae, ranging from learning and behavioral disorders to deafness, seizures, and motor deficits in 13% of cases [4, 15, 29, 32, 34, 39, 40].

The occurrence of negative consequences of bacterial meningitis in developed countries is strongly reduced by vaccination strategies, antibiotic treatment, and good care facilities [3, 9, 16]. The three leading causes of bacterial meningitis (*S. pneumoniae*, *N. meningitidis* and *H. influenzae*) are

vaccine preventable, and routine use of conjugate vaccines could provide substantial health and economic benefits through the prevention of childhood meningitis cases, deaths and disability [41, 42].

Few data sources are available to assess risk of neurological complications and long term sequelae from bacterial meningitis. Knowledge of the entire clinical spectrum of complications and their prompt detection are a prerequisite for the improved management of the disease [43].

This chapter summarizes the spectrum of early neurological complications as well the long-term sequelas of bacterial meningitis. Also we have evaluated the risks of early neurological complications and long term sequelae caused by bacterial meningitis, estimate the distribution of the different types of neurological complications and sequelae, and compare risk by age distribution and income. The study presents the review of published papers.

Complications of Bacterial Meningitis

The risk of death or developing complications from bacterial meningitis is related to the age and underlying condition of the patient, the causative pathogen, the severity and duration of illness at the time of presentation, and, occasionally, delays in the initiation of antibiotic therapy [3, 32, 36, 40, 41].

Two third of all pediatric deaths due to meningitis occur in low income countries and as many as 50% survivors of childhood meningitis experience long term neurological and neuropsychological sequelae [3, 9, 15, 17, 18, 19, 20, 24, 32, 40, 41, 42, 45, 46, 47].

Risks of long-term disabling sequelae are highest in low-income countries, where the burden of bacterial meningitis is greatest [29]. A major cause of sequelae of bacterial meningitis is intracranial complications arising during the acute phase of the disease. Complications due to bacterial meningitis can be divided into systemic and neurological.

Systemic complications such as septic shock, disseminated intravascular coagulation, acute respiratory distress syndrome, pericardial effusion, hypothalamic and other endocrine dysfunction, hyponatremia, bilateral adrenal hemorrhage and septic or reactive arthritis are usually the consequence of the bacteremia that frequently accompanies meningitis [47].

Neurological Complications of Bacterial Meningitis

Bacterial meningitis is a medical, neurological, and sometimes neurosurgical emergency that requires a multidisciplinary approach. Neurological complications of meningitis can occur at any time during the course of the disease. The incidence of neurological complications from bacterial meningitis varies by age distribution and income.

The risk of mortality and long term sequelae is higher in those individuals who develop acute neurological complications during the course of the disease. The highest risk for acute neurological complications occurred in infants and also in this age group was observed the highest incidence of long-term sequelae [48].

Common neurological complications of bacterial meningitis include:

- Impaired mental status
- Cerebral edema and increased intracranial pressure
- Seizures
- Subdural collections (subdural effusion, subdural hematoma or empyema)
- Cerebritis and cerebral abscess
- Hydrocephalus
- Focal neurological deficits (hearing impairment, cranial nerve palsies, hemiparesis or quadriparesis)
- Cerebrovascular abnormalities
- Ventriculitis
- Neuropsychological impairment and developmental disability
- Hypothalamic dysfunction

Neurological complications may be sudden or gradual in onset and can appear at any time after the onset of symptoms, including after the completion of therapy [15, 19, 30].

"Acute neurological complications" are defined as those arising during the acute phase of the disease and intensive care therapy. The diagnosis of neurological complications of bacterial meningitis is made by neurological examination, neuroimaging, electroencephalography and by neurologist, ophthalmologist, ENT specialist and psychologist evaluation. Indications for

performing neuroimaging (computed tomography or magnetic resonance imaging) following meningitis are: prolonged fever, focal neurological deficit, seizures (recurrent seizures, prolonged or difficult-to-control seizures, seizures late in the course of disease, and focal seizures), worsening consciousness level, prolonged cyto-biochemical changes in CSF or worsening clinical presentation. Although many neurological complications are severe, others, such as hearing loss, may be subtle or inapparent during the early phases of infection.

Incidence

Infants, the elderly, immunosuppressed patients and patients with chronic debilitating diseases are predisposed to bacterial meningitis.

The incidence of neurological complications from bacterial meningitis has varied widely in different studies. In one large study, 28 percent of episodes of community-acquired bacterial meningitis in adults resulted in one or more neurological complication, but no distinction was made between transient and long-term complications [30]. In another series, 21 percent of 277 adult patients developed a neurological deficit during the course of their illness, but this deficit persisted in only 9 percent of patients by the time of discharge [49].

Several studies reported cerebrovascular complications to be the most frequent complications of bacterial meningitis in adults and prognostic factors of the disease. From a prospective study of 86 adult patients with bacterial meningitis, half of patients had complications during the acute phase of meningitis; 35 patients had CNS complications, 19 had systemic complications 11 had both. The major central nervous system complications included angiographically documented cerebrovascular involvement (15.1%), brain swelling (14.0%), hydrocephalus (11.6%), and intracerebral hemorrhage (2.3%), while septic shock (11.6%), adult respiratory distress syndrome (3.5%), and disseminated intravascular coagulation (8.1%) dominated among the patients with systemic complications [47].

From a study of pneumococcal meningitis in adults, meningitis associated intracranial complications developed in 74.7% and systemic complications in 37.9% of cases [48]. Diffuse brain edema (28.7%) and hydrocephalus (16.1%) developed more frequently than previously reported [50]. The incidences of arterial (21.8%) and venous (9.2%) cerebrovascular complications were also very high. Furthermore, 9.2% of cases developed spontaneous intracranial

haemorrhages [50]. A haematogenous pathogenesis seemed likely in asplenic patients, while contiguous spread from sinusitis or otitis was the major cause of meningitis in nonasplenic individuals [50].

A prospective study of predictors for neurological complications of bacterial meningitis in adults in a limited-resource country showed that meningitis associated intracranial complications developed in 17/46 patients (37%)[51]. The most frequent neurological complication was cerebral abscess in7/46 cases (15%) [51].

Most studies of the incidence of neurological complications of meningitis have been undertaken in children. In one pivotal study involving 97 children with Haemophilus influenzae meningitis, one or more acute neurological complications were common (52%), but persistent neurological sequelae occurred in only 14 children (11%) [52]. Sensorineural hearing loss was the most common permanent sequela (11 children), but seizures (2), hemiplegia (1) and mental retardation (1) were also observed. Permanent sensorineural hearing loss was reported in as many as 11 % of children in other studies [19, 53, 54].

From the retrospective study of children treated for bacterial meningitis in two study periods, in a developing country, of the 277 vs. 77 children treated for bacterial meningitis, 22 % vs. 43 % of the patients developed early neurological complications [48]. The most frequent early neurologic complications were: subdural effusions (13% vs. 29%), recurrent seizures (11% vs. 8%) and hydrocephalus (3% vs. 3%) [48]. The highest incidence of neurological complications occurred in cases caused by *H. influenzae* vs. *S. pneumoniae* although *meningococcus* was the leading causative pathogen of bacterial meningitis in children [48].

Rates of severe or moderate disability reported in one large study of long-term effects in infants ranged from 9% for meningococcal meningitis to 24% for pneumococcal meningitis [55].

From a prospective study of 77 children, treated for bacterial meningitis, age less than 12 months and severity of clinical presentation at admission have been identified as the strongest predictors of neurological complications and may be of value in selecting patients for more intensive care and treatment [56]. The highest risk for acute neurological complications occurred in infants and also in this age group was observed the highest incidence of long-term sequelae [56]. Anderson V. et al. showed that children with a history of meningitis are at greater risk for impairment in these areas, with experience of the disease prior to 12 months of age being an important risk factor [57].

Impaired Mental Status

Impaired mental status is experienced by most patients at presentation [47, 49, 51, 58]. A common cause of a decline in consciousness in bacterial meningitis is clinical evidence of meningoencephalitis (Figure 1) [59].

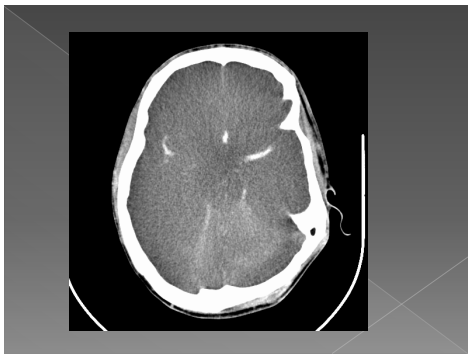

Figure 1. CT scan: Bacterial meningoencephalitis.

Increased intracranial pressure (ICP) is one of the major causes of altered mental status. Seizures and acute hydrocephalus are other frequent causes of deteriorating consciousness [30, 37]. A decreased level of consciousness, especially coma have been identified as important risk factors associated with poor outcome of bacterial meningitis in both children and adults [4, 26, 49, 51, 60, 61, 62, 63]. In children impaired consciousness and especially coma were one of the most important factors correlated with death among children with bacterial meningitis [24, 26, 63, 64, 65]. A study of 654 children with bacterial meningitis showed that the level of consciousness is the most important predictor of death and/or neurological sequelae, more than is etiology per se [27]. For patients with a decline in consciousness, or those whose condition fails to improve after the initiation of appropriate antimicrobial therapy, brain imaging is indicated.

Cerebral Edema and Increased Intracranial Pressure

The majority of patients with bacterial meningitis develop brain edema, which is manifested by signs and symptoms such as: impaired mental status up

to coma, bradycardia with hypertension, papilledema sometimes with loss of vision, cranial nerve palsy mostly the VI th nerve, and herniation of cerebellar tonsils, which may lead to death [30, 47].

The release of proinflammatory mediators in the subarachnoid space leads to an inflammatory response in the central nervous system that contributes to an increased permeability of the blood–brain barrier, cerebral edema, and increased intracranial pressure [59].

Brain edema can be caused by vasogenic, interstitial and cytotoxic mechanism [66, 67]. Vasogenic cerebral edema is primarily due to increased permeability of the blood brain barrier [67]. Cytotoxic factors released from neutrophils and bacteria may also directly produce cerebral edema. The inflammation produced by the infection can also directly impede the normal interstitial flow of CSF from the subarachnoid space [67]. In a prospective study of adults with bacterial meningitis, cerebral edema was detected by neuroimaging in 14% of patients [47].

Seizures

Seizures may occur as part of the clinical presentation of bacterial meningitis and are more often seen during the acute episode of the disease [47, 49, 58]. Fever, greater bacterial colony counts in CSF, bacterial toxins or secondary neurochemical changes are the cause of most seizures in patients with bacterial meningitis. Seizures occur in one-third to one-fourth of children with acute bacterial meningitis [48, 68]. Seizures have also been reported in 23 percent of adults with community-acquired bacterial meningitis [30].

From a retrospective study of the 277 children treated for bacterial meningitis, 60 children (22%) manifested seizures prior to admission, 57 children (21%) had seizures after admission; late seizures were diagnosed in 24 children (9%) [69]. Seizures prior to admission were predictors of high risk of adverse outcome in bacterial meningitis in children [69]. All children who manifested late seizures (those occurring >72 hours after admission) were diagnosed with meningitis related acute neurological complications; subdural effusion (18), hydrocephalus (6), intracranial bleeding (1) and subdural empyema (2) [48]. In another study, seizures were reported in 58/185 children (31%) during the acute phase of bacterial meningitis [68]. Prolonged or difficult-to-control seizures, seizures late in the course of disease, and focal

seizures are more likely to be associated with neurological sequelae [25, 26, 48, 60, 61, 69, 70].

Subdural Collections

Subdural collections are common neurological complications during the acute phase of bacterial meningitis in children with subdural effusion being the most frequent. Subdural fluid collection is a classic complication of bacterial meningitis in infants. When a diagnosis is based solely on subdural puncture, subdural effusion prevalence is estimated to be as high as 50%, with *H. influenzae* being the most common causative pathogen [71, 72]. Based on previous publications, subdural effusion is usually found in 40-60% of infants with bacterial meningitis [71, 72, 73].

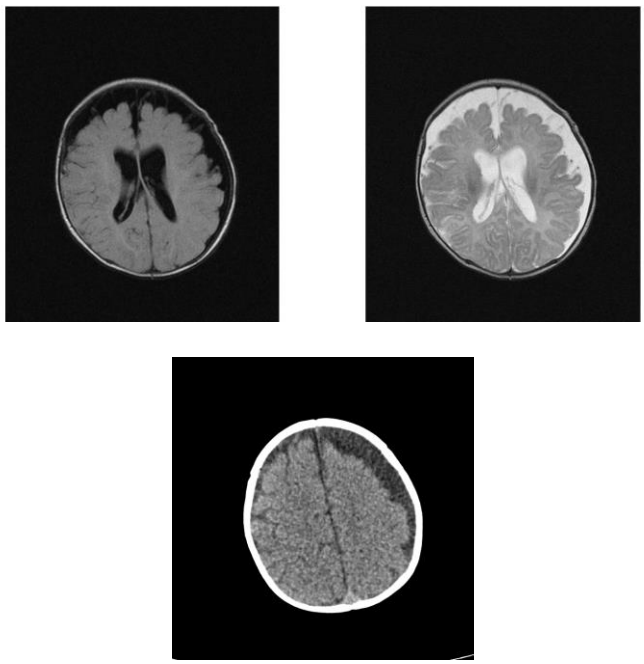

Figure 2. MRI images showing subdural effusions.

From the retrospective study of children treated for bacterial meningitis in two study periods, of the 277 vs. 77 children treated for bacterial meningitis, subdural effusion was the most frequent early neurological complication in

infants (26% vs. 61%) in both study periods [48]. Using a head CT scan, every third (35/109) vs. second child (22/45) was diagnosed with subdural effusion (Figure 1)[48].

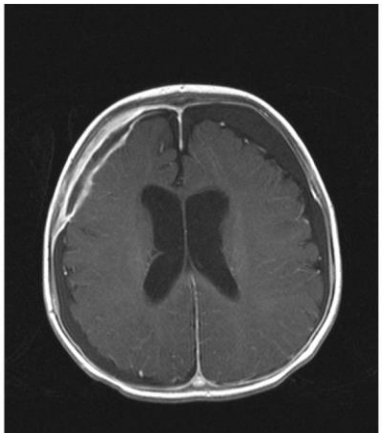

Figure 3. MRI images showing sudural empyema (right) and subdural effusion (left).

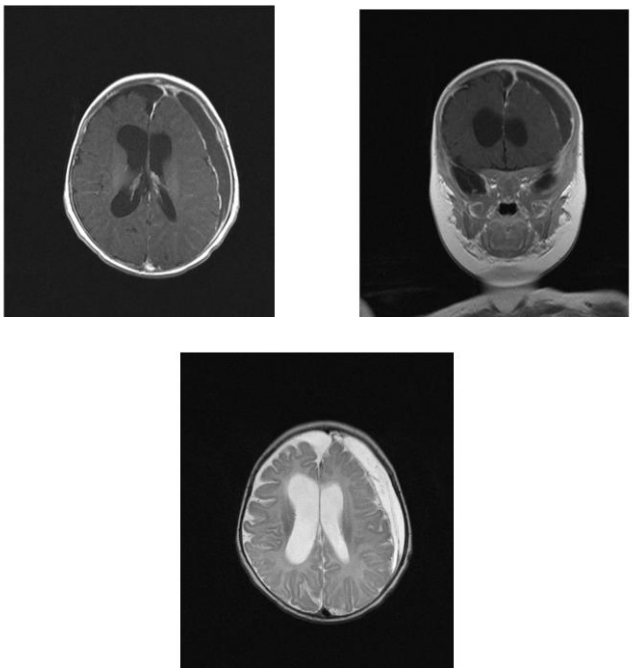

Figure 4. MRI images of subdural hematoma.

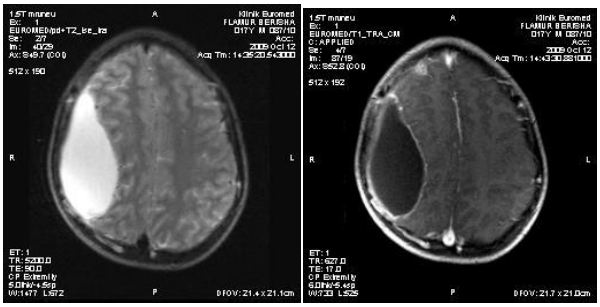

Figure 5. MRI images of subdural empyema.

The other subdural collections complicating bacterial meningitis in children were rare: subdural empyema 0.7 % vs. 1.3 % and subdural hematoma 0.4 % vs. 1.3% (Figure 4 and 5.). Subdural effusions rarely occur in adults with bacterial meningitis. In a prospective study of complications during bacterial meningitis in adults the authors did not observe any subdural fluid collection [47].

Cerebritis and Cerebral Abscess

Cerebritis is the initial parenchymal inflammation of the brain that normally leads to the formation of an abscess within the brain. Brain abscess is a focal, intracerebral infection that begins as a localized area of cerebritis and develops into a collection of pus surrounded by a well-vascularized capsule. Most of cases of brain abscess occur in adults from 30 to 40 years, while in patients younger than 2 years is extremely rare, exept in neonatal age related to the infection due to gram-negative bacilli.

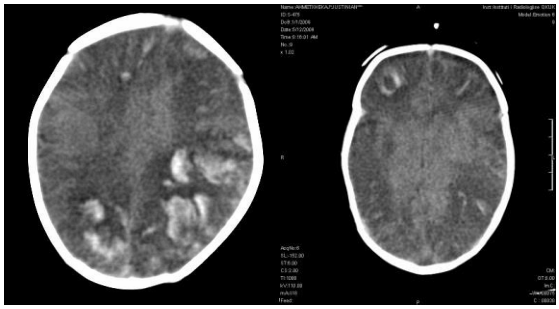

Figure 6. CT images showing multiple intracerebral bleedings and abscesses.

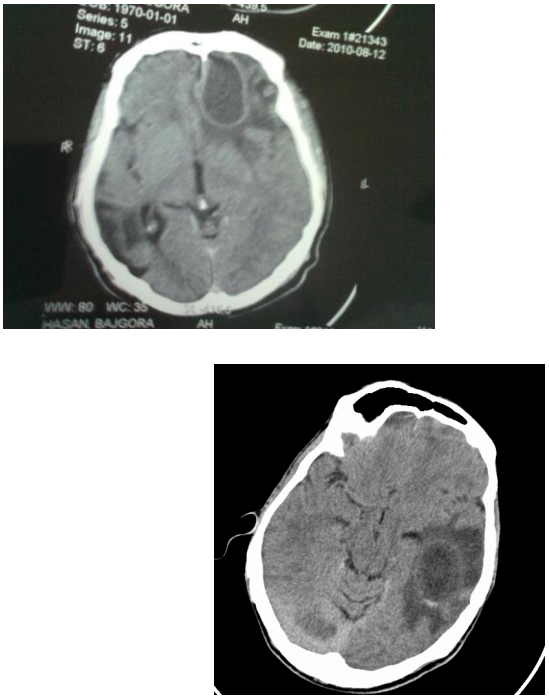

Figure 7. CT images of Brain abscesses.

From a study of children treated for bacterial meningitis in two study periods, of the 277 vs. 77 children treated for bacterial meningitis, cerebritis was observed in 0.4 vs. 3.9 percent of children while cerebral abscess was found only in one child 30 days old with pseudomonas meningitis (1.3%) during the second study period (Figure 6) [48]. Brain abscess is a rare complication of bacterial meningitis in adults usually in those having parameningeal focus of infection (ear, sinus or eye infection) or by hematogenous spread (Figure 7).

From a prospective study of prognostic factors for neurological complications of bacterial meningitis in adults, cerebral abscess was the most frequent neurological complication in 7/46 patients (15%) [51]. Adequate abscess drainage and appropriate antimicrobial therapy remain the cornerstones of proper treatment of brain abscess [74].

Hydrocephalus

Hydrocephalus in one of the severest complication of bacterial meningitis. It is usually presented as a communicating hydrocephalus during bacterial meningitis and is not a common complication beyond the neonatal period. Hydrocephalus is observed throughout the first 2 weeks of disease although it may already be present on the first day of disease and may provoke a life-threatening condition due to increased intracranial pressure and cerebral herniation. From a retrospective study of children treated for bacterial meningitis in two study periods, of the 277 vs. 77 children treated for bacterial meningitis, hydrocephalus was observed almost equally in both study periods, 2.5 vs. 2.6 percent (Figure 8) [48]. In this study, hydrocephalus was found to be the third most common neurological complication after subdural effusions (13% vs. 29%) and recurrent seizures (11% vs. 8%). Late admission was significantly associated with higher incidence of hydrocephalus. From long follow up, children with hydrocephalus had the worst prognosis. From this prospective study, the incidence of hydrocephalus was found to be much lower compared to the reported rate from many previous studies. A systematic review from 2010 analysed the global risk of neurological sequelae from bacterial meningitis in patients older than 1 month and found an overall rate of hydrocephalus of 7.1% [29]. The North Denmark retrospective study reported hydrocephalus in 3% of community-acquired bacterial meningitis with case fatality rate of 60% [75]. A Dutch national prospective cohort study reported a cumulative rate of hydrocephalus of 5% in adult community-acquired bacterial meningitis patients with case fatality rate of 50% [76]. A retrospective single centre study from Taiwan observed a cumulative rate of hydrocephalus of 21% with the overall mortality rate of 50% [77].

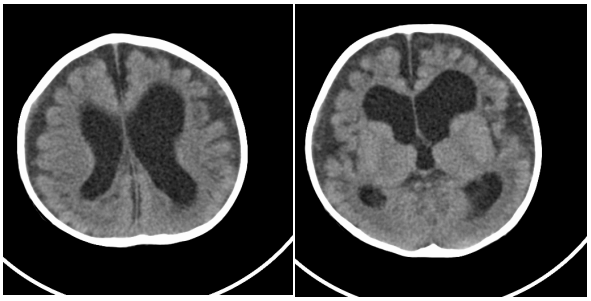

Figure 8. CT images showing obstructive hydrocephalus and subdural effusion.

In a prospective study of complications during bacterial meningitis in adults, the hydrocephalus was observed in 11.6 percent of patients [47]. The diagnosis of noncommunicating hydrocephalus and the decision for surgical treatment of hydrocephalus should be a multidisciplinary approach made by neurosurgeon, infectious diseases specialist, neurologist and ophthalmologist.

Focal Neurological Deficits (Hearing Impairment, Cranial Nerve Palsies, Hemiparesis or Quadriparesis)

Sensorineural hearing loss is the most common severe consequence of childhood bacterial meningitis, affecting approximately 9% of the children [31, 78 - 81]. Sensorineural hearing loss after bacterial meningitis may be due to damage to the cochlea, labyrinth, or eighth cranial nerve from direct bacterial invasion or the inflammatory response elicited by the infection [40]. It may be transient or permanent.

According to previous reports, hearing impairment of any type is expected to develop in 5.6% to 30.6% of patients with bacterial meningitis, while severe, profound or bilateral hearing loss is expected to occur in 1.0 to 5.1% of patients [14, 15, 82, 83, 84].

From the systematic literature review of the long-term (≥5 years of follow-up) sequelae of childhood bacterial meningitis, hearing changes accounted for 6.7 percent of patients [85]. In a study of 115 patients with bacterial meningitis, dexamethasone administered 10 minutes prior to antibiotics decreased the incidence of hearing loss and other neurological sequelae 15 months following the episode compared to antibiotics alone (5 versus 16 percent) [54].

From a study of long term sequelae of children treated for bacterial meningitis in two study periods, of the 277 vs. 77 children, deafness was observed in 1percent vs. 3 percent of children [48].

Sensorineural hearing impairment usually is not appreciated until the patient has recovered from the acute illness especially in infants. The inclusion of hearing evaluation in the routine follow-up of these children after bacterial meningitis may prevent missed diagnoses of hearing loss [19]. Early identification and rehabilitation of hearing loss is essential for the acquisition of normal speech and language, as well as for the child’s educational and social development [86].

Focal neurological deficit which can be manifested as cranial neuropathies, hemiparesis, quadriparesis, monoparesis, aphasia are common complications of meningitis. It can occur in 10 – 20% of patients with acute bacterial meningitis [30, 37]. Abnormalities of the cranial nerves are caused by the meningeal inflammatory process or by an increase in cerebrospinal fluid pressure. Focal neurological deficits account for most of the common complication of meningitis and it may account up to 50 percent of all neurological complication.

The cranial nerves most commonly affected are VI, III, IV and VII [30, 37]. Most such deficits resolve with successful treatment of the meningitis, but long-term disability may occur in some patients. From a study of early neurologic complications of children treated for bacterial meningitis in two study periods, the presence of neurologic deficit was observed by clinical examination in 16 percent vs. 17 percent of children. The observed neurologic deficit was reversible in all patients except in 0.4 percent vs. 1.3 percent of patients (quadriparesis/hemiparesis) [48].

Hemiparesis or Quadriparesis

Focal deficit as hemiparesis, monoparesis or quadriparesis are most commonly caused by cerebrovascular abnormalities, subdural effusion or empyema, hydrocephalus, cerebral abscess or cerebral edema. Paresis generally improves with time. Quadriparesis/hemiparesis was observed only in 0.4 percent vs. 1.3 percent of treated children with bacterial meningitis in two study periods [48]. From the prospective studies of risk factors for neurological complications in children and adults, haemiparesis was observed in 5/77 children (6.5%) and in 3/46 adults (6.5%) [51, 56].

Cerebrovascular Abnormalities

Thrombosis, vasculitis, ischemia, thromboembolism, thrombosis of superior sagittal sinus and cortical veins, acute cerebral bleeding or infarction, cerebral vessel anomalies like aneurysm and vasculitis are common cerebrovascular complications of bacterial meningitis.

Although cerebrovascular involvement in the acute phase of inflammation may be particularly important for the still unacceptably high morbidity and

mortality, only, a few studies have investigated cerebrovascular changes in bacterial meningitis [87].

From a prospective study of adults with bacterial meningitis, the major central nervous system complications included angiographically documented cerebrovascular involvement in 15.1 percent of patients [88]. Cerebrovascular complications observed in this study were: arterial narrowing, vessel wall irregularities, focal dilatations, arterial occlusions, thrombosis of venous sinuses and cortical veins. A poor clinical outcome of patients with bacterial meningitis, was significantly related to severe vascular involvement [87].

Ventriculitis

Ventriculitits is caused by infection of the ventricles, leading to swelling and inflammation. This is especially prevalent in patients with external ventricular drains and intraventricular stents.

Neuropsychological Impairment and Developmental Disability

It is well-known that moderate or severe mental retardation and development disability such as impairment of language, learning, behavioral and cognitive skills, may be a complication of bacterial meningitis in children. Cognitive impairment in adults is the commonest intellectual impairment in post meningitis patients.

Mild to severe mental retardation has been a well-recognized complication of bacterial meningitis in children, but few studies have utilized appropriate controls and sufficient follow-up to assess the risk of such complications. From a systematic literature search, of the total of 1433 children who were survivors of childhood bacterial meningitis, 49.2 percent were reported to have 1 or more long-term sequelae. A majority of childhood bacterial meningitis survivors with long-term sequelae that are documented in the literature (45%) had academic and behavioral limitations [85]. While neurological deficits may resolve over time, subtle behavioral deficits may not be appreciated initially and may continue to affect survivors for many years [85]. Further studies are needed to quantify the true societal and economic burden of long-term sequelae as well as fully understand the breadth of types of sequelae that

survivors experience [85]. From a study of children treated for bacterial meningitis in two study periods, neuropsychological impairment was observed in 1 percent vs. 5 percent of children [48].

Hypothalamic Dysfunction

The syndromes of inappropriate antidiuretic hormone secretion (SIADH) are a cause of hyponatremia is patients with disorders of the central nervous system [89]. In a study of sixty children, SIADH was diagnosed in 22 out of 60 cases (36.7%) on admission and in six of 48 cases (12.5%) on day 3 [90]. A significant correlation with SIADH was observed in cases with evidence of severe meningeal inflammation and mortality was significantly higher in cases with SIADH [90].

Unusual Complications

Transverse myelitis, cortical visual impairment, aneurysm formation of focal intracranial vessels, cerebral cortical atrophy, aphasia and ataxia are rare neurological complications of meningitis.

Surgical Treatment of Neurological Complications of Bacterial Meningitis

Bacterial meningitis is a medical, neurological, and sometimes neurosurgical emergency that requires a multidisciplinary approach. Prolonged fever, focal neurological deficit, convulsions, worsening of consciousness level and worsening of clinical presentation following meningitis are the absolute indications for performing the diagnostic imaging techniques. Magnetic resonance imaging (MRI) does not use ionizing radiation, and is thus preferred over Computed tomography (CT) in children and patients requiring multiple imaging examinations. In all cases of bacterial meningitis complicated with neurological complications in which a significant mass effect is apparent on imaging and by clinical presentation, an adequate treatment consists of prompt systemic administration of antibiotics combined with surgical treatment.

From a study of the 277 children treated for bacterial meningitis, due to the suspicion for neurological complications, 109 children underwent a head computerized tomography scan. 47 cases (43%) had evident structural abnormalities while only 15/277 cases (5%) required neurosurgical treatment; 9/38 cases with subdural collections, 5/7 cases with hydrocephalus and 1 case of spinal abscess [91]. Subdural effsions were the most common acute neurological complications of bacterial meningitis in children: 35 children with subdural effusion, 2 children with subdural empyema and 1 case with subdural hematoma. Of the 35 cases with subdural effusion, six cases (17%) underwent surgical treatment during the first week of treatment (mean time, day 5) due to worsening clinical presentation with space-occupying symptoms and signs [91]. The surgical techniques applied were surgical burr hole drainage in five cases and the placement of a subduroperitoneal shunt in one case. Of the 35 cases with subdural effusions, 29 children were treated conservatively and showed spontaneous remission of subdural effusion on repeated head CT scans [91]. The etiology of cases with subdural effusion was confirmed in 27/35 cases (77.1%). Causative pathogens were: *Neisserria meningitidis* (11/35), *Haemophillus influenzae* (6/35), *Streptococcus pneumoniae* (6/35), *Staphylococcus aureus* (2/35) and *gram negative bacilli* (2/35). All 35 children with subdural effusion were observed for 5 years, and the only complication and sequelae observed were seizures in 2 children, both treated conservatively. Neurosurgical intervention were not common in pediatric bacterial meningitis cases (5%) but were highly significant in cases complicated with acute neurological complications (32%) [91].

Long-Term Prognosis of Bacterial Meningitis

While early neurological complications may resolve over time, numerous long term sequelae have been reported in survivors of bacterial meningitis. *"Sequelae"* are defined as complications that result from bacterial meningitis that are present at or develop after the time of discharge and persist during the years follow-up period.

As many as 50% of survivors experience neurological sequelae, such as seizure disorders, focal neurological deficits, hearing/vision loss, and neuropsychological impairment. From a systematic review, cognitive deficit, bilateral hearing loss, motor deficit, seizures, visual impairment,

hydrocephalus were labelled as major sequelae [85]. Less severe, minor sequelae were labeled behavioral problems, learning difficulties, unilateral hearing loss, hypotonia, diplopia.

Numerous sequelae have been observed in survivors of childhood bacterial meningitis including seizure disorders, hearing/vision loss, hydrocephalus, focal neurological deficit, motor delay and impairment as well as more subtle outcomes like cognitive, academic and behavioral problems [44, 48, 69].

Chandran A. et al. in their systematic literature search have found that 49 % of survivors of childhood bacterial meningitis (followed up for at least five years) were reported to have one or more long-term sequelae [85]. A majority of reported sequelae were behavioral and/or intellectual disorders (78 %) most commonly low IQ or "cognitive impairment". Other problems in this category included behavioral problems and attention deficit hyperactivity disorder [85]. Most of the remaining sequelae were hearing impairments (6.7%) and major neurological abnormalities (14.3%).

The risk of long term sequelae is higher in those individuals who have acute neurological complications during the course of the disease [23, 39, 48].

From a retrospective study of children treated for bacterial meningitis in two study periods, long term sequelae were observed almost equally in 10% vs. 12% of children [48]. The most frequent long term sequelae were late seizures 9% vs. 1%, neuropsychological impairment 1% vs. 5% and deafness 1% vs. 3% [48]. Age prior to 12 months was risk factor for both early neurological complications and long-term sequelae of bacterial meningitis in children.

In a prospective study of adverse outcomes of bacterial meningitis in school-age survivors, one in four school-age meningitis survivors has either serious and disabling sequelae or a functionally important behavior disorder, neuropsychological or auditory dysfunction adversely affecting academic performance [92]. All survivors from bacterial meningitis, require careful follow-up, at least until school age [92].From data from a Greek meningitis registry, of a total of 2.477 patients, rate of sequelae overall (3.3%), is lower when compared to other reports in the literature, which ranges from 8% to 37% - with an average around 15% to 17.5% [15, 20, 61, 62, 68, 92, 93, 94]. According to previous reports, hearing impairment of any type is expected to develop in 5.6% to 30.6% of patients with bacterial meningitis, while severe, profound or bilateral hearing loss is expected to occur in 1.0 to 5.1% of patients [15, 20, 31, 82, 83, 84, 95]. From a retrospective study of long term sequelae of children treated for bacterial meningitis in two study periods,

deafness occurred in 1 percent vs. 3 percent of patients [48]. Many authors reported that occurrence of seizures on admission were strongly associated with the development of seizure disorder as a sequelae, and especially atypical seizures and those occurring after 48 hours after admission [20, 33, 48, 61, 62, 93].

Rates of sequelae are reported to be less common in meningococcal meningitis compared to pneumococcal meningitis [55].

Mortality/Morbidity

In general, mortality rates vary with age and pathogen. The leading cause of acute bacterial meningitis in adults is *Streptococcus pneumoniae*, with a mortality of 20–30% despite highly effective antibiotic therapy and modern intensive care facilities [4, 30]. Many fatalities are due to cerebral complications (e.g., brain edema, hydrocephalus, ischemic infarction and septic sinus or venous thrombosis) or systemic complications (e.g., septic shock, disseminated intravascular coagulation and adult respiratory distress syndrome) [4, 47]. From a study of pneumococcal meningitis in adults, the causes of death were mostly systemic complications in the elderly and cerebral complications in the younger patients [50].

Despite effective antimicrobial and supportive therapy, mortality rates among neonates remain high, with significant long-term sequelae in survivors. Bacterial meningitis also causes long-term sequelae and results in significant morbidity beyond the neonatal period. Mortality rates are highest during the first year of life, decreasing in mid life and increasing again in elderly persons.

Despite advances in care for patients with bacterial meningitis, the overall case fatality remains steady at approximately 2% - 30% [2, 3, 30 - 38]. The factors that impact mortality rates include access to primary health care services, the quality of reference laboratories, timely and appropriate medical care and treatment, patient predisposing conditions, and the virulence of the strains [26, 27, 35, 37, 49, 51, 62, 63, 96].

Risk Factors for Adverse Outcome

Several studies of prognostic factors in patients with bacterial meningitis have been performed [2, 15, 17, 19, 20, 21, 23, 26, 28, 29, 33, 37, 39, 45, 48,

49, 60, 61, 62, 63, 64, 69, 70, 81, 90, 97]. The majority of all studies were conducted in developed countries.

Identification of predictors for early neurological complications is extremely important since they are first messengers in predicting also long term sequelae of childhood bacterial meningitis [48].

For mortality, coma and seizures were found to be predictive, next to shock, peripheral circulatory failure, severe respiratory distress, a low peripheral white blood cell count and a high cerebrospinal fluid protein level [17, 22, 32, 33].

From a prospective study in a developing country, risk factors found to be associated with death among children treated for bacterial meningitis were: the presentation of the initial cerebrospinal fluid as thick pus, low cerebrospinal fluid /blood glucose ratio, a decreased level of consciousness especially coma, the occurrence of seizures both prior to hospitalization and >24hours after admission, age less than <1 month, use of inotropic agents on admission, presence of focal neurological deficit on admission, previous treatment with antibiotics, female gender and preceding hospitalization before being diagnosed for bacterial meningitis [24].

Studies reporting on poor outcome, and thereby not differentiating between sequelae or mortality, also reported coma, seizures, shock, use of inotropes, *S.pneumoniae* infection, acute focal neurological symptoms, a low white blood cell count both peripheral as well as in cerebrospinal fluid, a low cerebrospinal fluid glucose level and a high cerebrospinal fluid protein level to be important risk factors [15, 17, 98, 99]. Other risk factors identified by previous studies include: young age (indicated as younger than 12 months), tertiary referral, symptoms > 24 h before diagnosis, delayed sterilization of the cerebrospinal fluid, early admission to the intensive care unit, requirement of assisted ventilation, dexamethasone use, the presence of a primary focus of infection and the presence of underlying disease [15, 17, 22, 32, 33, 39, 54, 56, 64, 97].

Klinger G. et al. found that duration of seizures for >72 hours, presence of coma, use of inotropes, and leucopenia were the most important predictors of adverse outcome [99].

Oostenbrik R. et al. (2002) found that children with bacterial meningitis caused by *Streptococcus pneumoniae* and those with acute focal neurological symptoms tended to have the worst prognosis [15]. Grimwood K. et al. (1996) found that age <= 12 months, tertiary referral, symptoms > 24 h before diagnosis, seizures, focal neurological signs, deteriorating conscious state in

hospital, Streptococcus pneumoniae infection and serum sodium concentration < 130 mmol/L were associated with adverse outcomes [61].

Severity of clinical presentation manifested with alteration of mental status and the occurrence of seizures are identified as the strongest prognostic factors for neurological complications in numerous studies from developed [15, 20, 22] and developing countries [23, 25, 26, 27, 28, 60].

From a prospective study of risk factors for neurological complications in childhood bacterial meningitis, as risk factors were found: age < 12 months, altered mental status, seizures prior to admission, dexamethasone use, the presence of focal neurological deficit on admission and increased proteins in CSF [56].

Young age (indicated as younger than two years old), is considered an important prognostic factor for adverse outcome of children with bacterial meningitis [17, 24, 28, 60].

In a study of mortality from bacterial meningitis in children in a developing country, the highest mortality rate was recorded in neonates, and the highest incidence of neurological complications was found in children who were <12 months of age [24].

Duration of seizures for >72 hours and presence of coma were the most important predictors of adverse outcome [15, 65].

Delay in treatment is associated with an increased risk of neurological disability and death in both developed [2, 32, 55] and developing countries [26, 27, 46, 100].

From a study of children with bacterial meningitis treated in a developing country, the mean duration of illness prior to hospitalization was 2.6 days for patients who recovered without neurological complications, 3.2 days for patients who survived with neurological complications, and 5.3 days for patients who died ($p<0.001$) [24, 60].

Aronin SI. et al. found that delay in therapy after arrival in the emergency department was associated with adverse clinical outcome when the patient's condition advanced to the highest stage of prognostic severity before the initial antibiotic dose was given [49].

Children who manifested focal neurological deficit at admission had a significantly higher incidence of neurological complications [15, 48].

Low CSF leukocyte count, low CSF glucose level, low CSF/blood glucose level and high CSF protein level have been identified as significant factors predicting neurological complications of bacterial meningitis in children in both developed [2,18, 19, 20, 21, 22, 76] and developing countries [25, 26, 27, 28, 76].

An association between meningitis caused by *S.pneumoniae* and unfavorable evolution has been suggested in the literature [2, 15, 19, 23, 26, 27, 31]. Even with early diagnosis and adequate treatment, the case fatality in pneumococcal meningitis is in the range of 19% - 37% [37, 50, 97].

From a study of children treated for bacterial meningitis in two study periods, in the first study period the highest incidence of neurological complications occurred in cases caused by *H. influenzae* since in this study Hib vaccine was not yet implemented in the national immunization programme [48]. In the second study period was implemented the Hib vaccine and in this study, the highest incidence of neurological complications occurred in cases caused by *S. pneumoniae* [48].

The presence of a primary focus of infection, previous treatment with antibiotics, female gender and location of residence (urban/rural location) were not found to be associated with increased risk for the development of neurological complications [60].

The severity of clinical presentation at admission involving the presence of focal neurological deficit, altered mental state, especially coma, and infection with gram negative-bacilli have been identified as the strongest predictors for neurological complications of bacterial meningitis in adults and may be of value in selecting patients for more intensive care and treatment [51].

Many clinical trials were undertaken to determine the effects of adjunctive dexamethasone on outcome in children with bacterial meningitis [16, 22, 24, 32]. The results, however, do not point unequivocally to a beneficial effect [16, 46].

The inflammatory response induced by bacterial products in the subarachnoid space is responsible for neuronal injury [97]. The use of adjuvant therapy in acute bacterial meningitis draws its rationale from the notion of arresting the inflammatory cascade at an early stage of the disease to improve clinical outcome. Corticosteroids have been studied extensively in these patients and seem effective in selective groups of patients, particularly those with pneumococcal meningitis [97].

Considerable evidence implicates that genetic variation in microbial recognition genes is associated with altered host responses to infection and the degree of post-infectious complications [101]. Genetic variation in innate immune response genes contributes to inter-individual differences in disease manifestation and degree of complications upon infection [102]. Genetic markers may be used for identification of high-risk patients by creating prediction rules for post-meningitis hearing loss and other sequelae, and

provide more insight in the complex immune response in the CNS possibly resulting in new therapeutic interventions [102].

Further Research

Few studies document sequelae for several years following a childhood episode of bacterial meningitis. In addition, studies generally focus on the more commonly found sequelae.

While neurological deficits may resolve over time, subtle behavioral deficits may not be appreciated initially and may continue to affect survivors for many years. Further studies are needed to quantify the burden of early neurological complications by age distribution, etiologic agents and income. Also further studies are needed to follow up long term sequelae in patients who manifested early neurological complications using control/comparison group patients who did not manifest neurological complications during the acute phase of illness. We recommend additional research for the relationship between intellectual, linguistic, learning, and reading skills with educational difficulty especially with children with a history of bacterial meningitis prior to 12 months of age being an important risk factor.

Prevention of bacterial meningitis by conjugate vaccines against *Haemophillus influenzae*, *Streptococcus pneumoniae* and *Neisseria meningitidis* will be the most promising development in future.

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