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RESEARCH ARTICLE

EARLY COMPLICATIONS OF ACUTE BACTERIAL MENINGITIS IN CHILDREN BEYOND NEONATAL PERIOD

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ABSTRACT

Background: Bacterial meningitis continues to be a serious, often disabling infectious disease, during the acute onset of meningitis, acute CNS complications can include seizures, increased intracranial pressure, cranial nerve palsies, stroke,cerebral or cerebellar herniation, and thrombosis of the dural venous sinuses, Long-term sequelae of meningitis result from direct inflammatory destruction of brain cells, vascular injuries, or secondary gliosis. Focal motor and sensory deficits, visual impairment, hearing loss, seizures, hydrocephalus, and a variety of cranial nerve deficits can result from meningitis, In addition to the variety of disorders mentioned earlier in this section; some patients with meningitis have mental retardation and severe behavioral disorders that limit their function at school and later performance in life.

Aim of study

- Early detection of possible post-meningitis complication.
- To find the prognostic factors of those complication.

Patient and method: Among one hundred twenty-three patients selected, One hundred fifteen patients enrolled in study after they met inclusion criteria, they are aged 1 month to 15 years, admitted to infectious department at Central teaching hospital of pediatrics in Baghdad/Iraq with acute bacterial meningitis, followed up after discharge over a 12 month period. Data were collected from the infectious follow up clinic in our center, Various data collected from history, examination, and investigation results for comparison to show the risk factors associated with developing complications. **Results:** Among one hundred fifteen cases enrolled in the study, Benign course patients (patients who developed no sequelae after meningitis) were 60 in number, complicated course patients were 55 in number, Prognostic factors found to be significantly related to the outcome in this study.these factors include:young age group (below 12 months) , prolonged seizure at presentation more than 72hours, various CSF parameters (CSF neutrophil predominance pleocytosis, high CSF protein more than 50mg/dl, low CSF glucose below than 40mg/dl, CSF culture positive results), a variety of serum laboratory findings (positive C-reactive protein more than 12, leukopenia below 4000), and Streptococcus pneumoniae in blood culture is considered important in predicting complications. **Conclusion:** In conclusion, the age of less than 12 months and the clinical presentation on admission (occurrence of seizures especially prolonged one), as well as multiple CSF and serum laboratory findings were identified as the strongest predictors of neurological complications and may have value predicting which patients are prone to complication.

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INTRODUCTION

Bacterial meningitis:- Infections of the CNS are among the most common neurologic disorders encountered by pediatricians. Although infections are among the CNS disorders most amenable to treatment, they also have a very high potential for causing catastrophic destruction of the nervous system. It is imperative for the clinician to recognize infections early in order to treat and prevent massive tissue destruction (Curtis et al., 2010). The presentation of various CNS infections is often nonspecific and includes fever, headache and altered sensorium, at times seizures and focal neurodeficits (Kim, 2010). Clues from a detailed history, epidemiology, examination and appropriate investigations are required for a precise diagnosis. [(2)] Meningitis implies primary involvement of the meninges, whereas encephalitis indicates brain parenchymal involvement. Because these anatomic boundaries are often not distinct, many patients have evidence of both meningeal and parenchymal involvement and should be considered to have meningoencephalitis.[(2)] Bacterial meningitis is one of the most potentially serious infections occurring in infants and older children. This infection is associated with a high rate of acute complications and risk of long-term morbidity (Kim, 2010).

Etiology: Many microorganisms can cause CNS infection. Nonetheless, specific pathogens are identifiable and are influenced by the age and immune status of the host and the

epidemiology of the pathogen. In general, viral infections of the CNS are much more common than bacterial infections, which, in turn, are more common than fungal and parasitic infections.[3] Infections caused by rickettsiae (Rocky Mountain spotted fever, Ehrlichia) are relatively uncommon but assume important roles under certain epidemiologic circumstances. Mycoplasma spp. can also cause infections of the CNS, although their precise contribution is often difficult to determine (Török, 2007). The most common causes of bacterial meningitis in children older than 1 mo of age in the United States are Streptococcus pneumoniae and Neisseria meningitidis. Bacterial meningitis caused by S. pneumonia and Haemophilusinfluenzae type b has become much less common in developed countries since the introduction of universal immunization against these pathogens beginning at 2 mo of age.[5] Infection caused by S. pneumoniae or H. influenzae type b must be considered in incompletely vaccinated individuals or those in developing countries (Radetsky, 1992). Those with certain underlying immunologic (HIV infection, immunoglobulin [Ig] G subclass deficiency) or anatomic (splenic dysfunction, cochlear defects or implants) disorders also may be at increased risk of infection caused by these bacteria (Roine et al., 2008). Alterations of host defense resulting from anatomic defects or immune deficits also increase the risk of meningitis from less-common pathogens such as Pseudomonas aeruginosa, Staphylococcus aureus, coagulase-negative staphylococci, Salmonella spp., anaerobes, and Listeria monocytogenes (Chávez-Bueno et al., 2005). The commonest route of meningeal infection is from the bloodstream, so the spectrum of pathogens causing meningitis is similar to that seen in bacteremia and sepsis. The introduction of the Haemophilus influenza type b (Hib) polysaccharide-conjugate vaccine into the UK vaccination program has had a dramatic effect (Saha et al., 2005). The incidence of Hib meningitis has dropped from around 2500 cases per year to 44 per year, with Neisseria meningitidis now the commonest cause of community acquired bacterial meningitis in the UK, followed by Streptococcus pneumoniae.

The relative importance of these pathogens varies considerably with age and the nature of the immunization programs in operation. In the neonatal period, group B streptococcus is the prominent meningeal pathogen, followed by Gram negative bacilli, S. pneumoniae and Listeria monocytogenes. In children older than 3 months and in young adults, the most frequent cause of bacterial meningitis is N. meningitidis followed by S. pneumoniae. Infants between 1 and 3 months old are susceptible to N. meningitidis and S. pneumoniae, as well as the neonatal pathogens. The propensity of neonates to get meningitis is in part due to their immunological immaturity.[10] Older children with congenital or acquired deficiencies in complement, immunoglobulin production, lymphocytes, neutrophils or splenic dysfunction are at increased risk from meningitis, sometimes due to atypical pathogens (De Cauwer, 2007). A rare but serious form of bacterial meningitis is caused by Mycobacterium tuberculosis. This organism can affect patients of all ages and should be considered in any atypical presentation of meningitis, particularly patients presenting with an insidious illness (Visintin, 2010) While meningitis often occurs in the context of systemic infections, it can also follow bacterial invasion from a contiguous focus of infection, such as

- The mastoids or paranasal sinuses,
- from osteomyelitis of the skull.
- Skull fractures,
- craniospinal dermal sinuses,
- neurenteric or dermoid cysts,
- Occult intranasal encephaloceles, or
- transethmoidmeningoceles are also potential portals of entry for pathogens into the subarachnoid space.
- The possibility of a cranial defect should be considered in children with recurrent meningitis.
- Neurosurgical procedures and the presence of ventriculoperitoneal shunts also provide routes for meningeal infection. In such cases, Staphylococcus aureus and coagulase negative staphylococci are more likely pathogens (Dubos et al., 2010).

Epidemiology: A major risk factor for meningitis is the lack of immunity to specific pathogens associated with young age. Additional risks include;

- Recent colonization with pathogenic bacteria,
- Close contact (household, daycare centers, college dormitories, military barracks) with individuals having invasive disease caused by N. meningitidis or H. influenza type b,
- Crowding,
- Poverty,
- Black or Native American race, and
- Male gender (Kim, 2010)

The mode of transmission is probably person-to-person contact through respiratory tract secretions or droplets. The risk of meningitis is increased among infants and young children with occult bacteremia; the odds ratio is greater for meningococcus (85 times) and H. influenzae type b (12 times) relative to that for pneumococcus (Cochrane Database of Systematic Reviews, 1996).

Pathology and pathophysiology: A meningeal purulent exudate of varying thickness may be distributed around the cerebral veins, venous sinuses, convexity of the brain, and cerebellum, and in the sulci, sylvian fissures, basal cisterns, and spinal cord. Ventriculitis with bacteria and inflammatory cells in ventricular fluid may be present (more often in neonates), as may subdural effusions and, rarely, empyema. Perivascular inflammatory infiltrates also may be present, and the ependymal membrane may be disrupted (Brouwer, 2012). Inflammation of spinal nerves and roots produces meningeal signs, and inflammation of the cranial nerves produces cranial neuropathies of optic, oculomotor, facial, and auditory nerves. Increased intracranial pressure (ICP) also produces oculomotor nerve palsy because of the presence of temporal lobe compression of the nerve during tentorial herniation. Abducent nerve palsy may be a nonlocalizing sign of elevated ICP.[16] Hydrocephalus can occur as an acute complication of bacterial meningitis. It most often takes the form of a communicating hydrocephalus caused by adhesive thickening of the arachnoid villi around the cisterns at the base of the brain. Thus, there is interference with the normal resorption of CSF. Less often, obstructive hydrocephalus develops after fibrosis and gliosis of the aqueduct of Sylvius or the foramina of Magendie and Luschka (Silvia, 2005). Damage to the cerebral cortex may be a result of the focal or diffuse effects of vascular occlusion (infarction, necrosis, lactic acidosis), hypoxia, bacterial invasion (cerebritis), toxic encephalopathy (bacterial toxins), elevated ICP, ventriculitis, and transudation (subdural effusions) (Shacham, 2009).

These pathologic factors result in the clinical manifestations of impaired consciousness, seizures, cranial nerve deficits, motor and sensory deficits, and later psychomotor retardation (Shacham, 2009).

Clinical Manifestations: The signs and symptoms of meningitis are related to the nonspecific findings associated with a systemic infection and to manifestations of meningeal irritation. Nonspecific findings include fever, anorexia and poor feeding, headache, symptoms of upper respiratory tract infection, myalgias, arthralgias, tachycardia, hypotension, and various cutaneous signs, such as petechiae, purpura, or an erythematous macular rash (Thigpen, 2011). Meningeal irritation is manifested as nuchal rigidity, back pain, Kernig sign (flexion of the hip 90 degrees with subsequent pain with extension of the leg), and Brudzinski sign (involuntary flexion of the knees and hips after passive flexion of the neck while supine). In children, particularly in those younger than 12-18 mo, Kernig and Brudzinski signs are not consistently present.

Tripod sign: In the sitting position, the child supports himself with both arms extended behind the back, which is kept straight.

Knee-kiss sign: The child cannot bend forward to kiss his knees (Brouwer et al., 2012). Indeed fever, headache, and nuchal rigidity are present in only 40% of adults with bacterial meningitis. Increased ICP is suggested by headache, emesis, bulging fontanel or diastasis (widening) of the sutures, oculomotor (anisocoria, ptosis) or abducent nerve paralysis, hypertension with bradycardia, apnea or hyperventilation, decorticate or decerebrate posturing, stupor, coma, or signs of herniation. Papilledema is uncommon in uncomplicated meningitis and should suggest a more chronic process, such as the presence of an intracranial abscess, subdural empyema, or occlusion of a dural venous sinus. Focal neurologic signs usually are a result of vascular occlusion (Cohen, 2017). Cranial neuropathies of the optic, oculomotor, abducent, facial, and auditory nerves may also be the result of focal inflammation. Overall, approximately 10-20% of children with bacterial meningitis have focal neurologic signs (Török, 2007). Seizures (focal or generalized) caused by cerebritis, infarction, or electrolyte disturbances occur in 20-30% of patients with meningitis. Seizures that occur on presentation or within the 1st 4 days of onset are usually of no prognostic significance. Seizures that persist after the 4th day of illness and those that are difficult to treat may be associated with a poor prognosis (Tunkel, 2004). Alterations of mental status are common among patients with meningitis and may be the consequence of increased ICP, cerebritis, or hypotension; manifestations include irritability, lethargy, stupor, obtundation, and coma. Comatose patients have a poor prognosis (Therapy of suspected bacterial meningitis in Canadian children six weeks of age and older, 2008). Additional manifestations of meningitis include photophobia and tachecérébrale, which is elicited by stroking the skin with a blunt object and observing a raised red streak within 30-60 sec (Cochrane Database of Systematic Reviews, 1996).

DIAGNOSIS: The diagnosis of acute pyogenic meningitis is confirmed by analysis of the CSF, which typically reveals microorganisms on Gram stain and culture, a neutrophilicpleocytosis, elevated protein, and reduced glucose concentrations. LP should be performed when meningitis is suspected (Dubos et al., 2010).

Contraindications for an immediate LP include:

- Evidence of increased ICP (other than a bulging fontanel), such as 3rd or 6th cranial nerve palsy with a depressed level of consciousness, or hypertension and bradycardia with respiratory abnormalities
- Severe cardiopulmonary compromise requiring prompt resuscitative measures for shock
- or in patients in whom positioning for the LP would further compromise cardiopulmonary function; and
- Infection of the skin overlying the site of the LP.

Thrombocytopenia is a relative contraindication for LP (Fouad et al., 2014). If an LP is delayed, empirical antibiotic therapy should be initiated. CT scanning for evidence of a brain abscess or increased ICP should not delay therapy. LP may be performed after increased ICP has been treated or a brain abscess has been excluded (Best et al., 2007). CT scan before the LP is not routinely needed; it is indicated in children with focal neurological symptoms or signs, papilledema, critically raised ICP or suspicion of a mass lesion. CT is normal in most cases of bacterial meningitis, including those with subsequent herniation; a normal CT does not rule out raised ICP.[7] Blood cultures should be performed in all patients with suspected meningitis. Blood cultures reveal the responsible bacteria in up to 80-90% of cases of meningitis. Elevations of the C-reactive protein, erythrocyte sedimentation rate, and procalcitonin have been used to differentiate bacterial (usually elevated) from viral causes of meningitis (Brouwer, 2012). A diagnostic conundrum in the evaluation of children with suspected bacterial meningitis is the analysis of CSF obtained from children already receiving antibiotic (usually oral) therapy. This is an important issue, because 25-50% of children being evaluated for bacterial meningitis are receiving oral antibiotics when their CSF is obtained (Ginsberg, 2004).

Differential Diagnosis: In addition to S. pneumoniae, N. meningitidis, and H. influenzaetype b, many other microorganisms can cause generalized infection of the CNS with similar clinical manifestations. These organisms include less typical bacteria, such as Mycobacterium tuberculosis, Nocardiaspp., Treponemapallidum(syphilis), and Borreliaburgdorferi (Lyme disease); fungi, such as those endemic to specific geographic areas (Coccidioides, Histoplasma, and Blastomyces) and those responsible for infections in compromised hosts (Candida, Cryptococcus, and Aspergillus); parasites, such as Toxoplasma gondiiand those that cause cysticercosis and, most frequently, viruses (Kim, 2010). Focal infections of the CNS including brain abscess and parameningeal abscess (subdural empyema, cranial and spinal epidural abscess) may also be confused with meningitis. In addition, noninfectious illnesses can cause generalized inflammation of the CNS. Relative to infections, these disorders are uncommon and include malignancy, collagen vascular syndromes, and exposure to toxins (Brouwer et al., 2012). In addition to bacterial, tuberculous, or fungal infection, the differential diagnosis also includes immune or inflammatory diseases such as Sweet syndrome, CNS vasculitis, sarcoidosis, lymphoma, and neonatal-onset multisystem inflammatory disease (Nigrovic, 2007). Acute viral meningoencephalitis is the most likely infection to be confused with bacterial meningitis. Although, in general, children with viral meningoencephalitis appear less ill than those with bacterial meningitis, both types of infection have a spectrum of severity.

Some children with bacterial meningitis may have relatively mild signs and symptoms, whereas some with viral meningoencephalitis may be critically ill. Although classic CSF profiles associated with bacterial vs viral infection tend to be distinct, specific test results may have considerable overlap (De Cauwer, 2007).

Treatment: The therapeutic approach to patients with presumed bacterial meningitis depends on the nature of the initial manifestations of the illness. A child with rapidly progressing disease of less than 24 hr duration, in the absence of increased ICP, should receive antibiotics as soon as possible after an LP is performed Lumbar puncture should be deferred in any child with a GCS of less than 13, focal symptoms or signs, papilledema or radiological evidence of raised ICP. A normal CT scan does not exclude raised ICP. Increased ICP should be treated simultaneously. Immediate treatment of associated multiple organ system failure, shock, and acute respiratory distress syndrome is also indicated (Bociaga-Jasik, 2003). Patients who have a more protracted subacute course and become ill over a 4-7 day period should also be evaluated for signs of increased ICP and focal neurologic deficits. Unilateral headache, papilledema, and other signs of increased ICP suggest a focal lesion, such as a brain or epidural abscess, or subdural empyema. Under these circumstances, antibiotic therapy should be initiated before LP and CT scanning. If signs of increased ICP and/or focal neurologic signs are present, CT scanning should be performed first to determine the safety of performing an LP (Ricard, 2007).

Initial Antibiotic Therapy: The initial (empirical) choice of therapy for meningitis in immunocompetent infants and children is primarily influenced by the antibiotic susceptibilities of S. pneumoniae. Selected antibiotics should achieve bactericidal levels in the CSF. Although there are substantial geographic differences in the frequency of resistance of S. pneumonia to antibiotics, rates are increasing throughout the world. In the United States, 25-50% of strains of S. pneumoniae are currently resistant to penicillin (van de Beek, 2012) Resistance to cefotaxime and ceftriaxone is also evident in up to 25% of isolates. In contrast, most strains of N. meningitidis are sensitive to penicillin and cephalosporins, although rare resistant isolates have been reported. Approximately 30-40% of isolates of H. influenzaetype b produce β-lactamases and, therefore, are resistant to ampicillin. These β-lactamase–producing strains are sensitive to the extended-spectrum cephalosporins (Cohen, 2017). Based on the substantial rate of resistance of S. pneumoniae to β-lactam drugs, vancomycin (60 mg/kg/24 hr, given every 6 hr) is recommended as part of initial empirical therapy (Ricard et al., 2007). Because of the efficacy of third-generation cephalosporins in the therapy of meningitis caused by sensitive S. pneumoniae, N. meningitidis, and H. influenzaetype b, cefotaxime (300 mg/kg/24 hr, given every 6 hr) or ceftriaxone (100 mg/kg/24 hr administered once per day or 50 mg/kg/dose, given every 12 hr) should also be used in initial empirical therapy.[27] Patients allergic to β-lactam antibiotics and >1 mo of age can be treated with chloramphenicol, 100 mg/kg/24 hr, given every 6 hr. Another option for patients with allergy to β-lactam antibiotics is a combination of vancomycin and rifampin. Alternatively, patients can be desensitized to the antibiotic (Wall, 2013). If L. monocytogenesinfection is suspected, as in young infants or those with a T-lymphocyte deficiency, ampicillin (200 mg/kg/24 hr, given in four divided doses) also should also be given because cephalosporins are inactive against L. monocytogenes. Intravenous trimethoprim-sulfamethoxazole is an alternative treatment for L. monocytogenes (Therapy of suspected bacterial meningitis in Canadian children six weeks of age and older, 2008). If a patient is immunocompromised and Gram-negative bacterial meningitis is suspected, initial therapy might include ceftazidime and an aminoglycoside or meropenem (Ginsberg, 2004).

Duration of antibiotic therapy: Therapy for uncomplicated penicillin-sensitive S. pneumoniae meningitis should be for 10-14 days with a third-generation cephalosporin or intravenous penicillin (400,000 units/kg/24 hr, given every 4-6 hr) (Wall et al., 2013). If the isolate is resistant to penicillin and the third-generation cephalosporin, therapy should be conjugated with vancomycin (Wall et al., 2013). Intravenous penicillin (300,000 units/kg/24 hr) for 5-7 days is the treatment of choice for uncomplicated N. meningitidis meningitis. Uncomplicated H. influenzaetype b meningitis should be treated for 7-10 days. Patients who receive intravenous or oral antibiotics before LP and who do not have an identifiable pathogen, but do have evidence of an acute bacterial infection on the basis of their CSF profile, should continue to receive therapy with ceftriaxone or cefotaxime for 7-10 days. If focal signs are present or the child does not respond to treatment, a parameningeal focus may be present and a CT or MRI scan should be performed (Bociaga-Jasik, 2003).

Corticosteroids: Rapid killing of bacteria in the CSF effectively sterilizes the meningeal infection but releases toxic cell products after cell lysis (cell wall endotoxin) that precipitate the cytokine-mediated inflammatory cascade.[30] Data support the use of intravenous dexamethasone, 0.15 mg/kg/dose given every 6 hr for 2 days, in the treatment of children older than 6 wk with acute bacterial meningitis caused by H. influenza type b. Among children with meningitis caused by H. influenza type b, corticosteroid recipients have a shorter duration of fever, lower CSF protein and lactate levels, and a reduction in sensorineural hearing loss.[31] Data in children regarding benefits, if any, of corticosteroids in the treatment of meningitis caused by other bacteria are inconclusive. Early steroid treatment of adults with bacterial meningitis, especially those with pneumococcal meningitis, results in improved outcome (Heckenberg, 2012).

Supportive Care: Hyponatremia is frequently observed in patients with bacterial meningitis. While this is associated with elevated serum antidiuretic hormone (ADH), possibly suggesting inappropriate ADH secretion (SIADH), more recent studies indicate that SIADH is overdiagnosed and the patients are hypovolemic (Køster-Rasmussen, 2008). Treatment of suspected SIADH with fluid restriction could potentially compromise circulating volume and therefore cerebral blood flow. Circulatory shock should be treated aggressively, significant dehydration corrected carefully, fluid balance monitored frequently and maintenance fluids given with care (Kumar et al., 2014). Patients should initially receive nothing by mouth. If a patient is judged to be normovolemic, with normal blood pressure, intravenous fluid administration should be restricted to one-half to two-thirds of maintenance, or 800-1,000 mL/m2/24 hr, until it can be established that increased ICP or SIADH is not present (Kumar et al., 2014). Fluid administration may be returned to normal (1,500-1,700 mL/m2/24 hr) when serum sodium levels are normal. Fluid restriction is not appropriate in the presence of systemic

hypotension because reduced blood pressure may result in reduced cerebral perfusion pressure and CNS ischemia. Therefore, shock must be treated aggressively to prevent brain and other organ dysfunction (acute tubular necrosis, acute respiratory distress syndrome) (Molyneux, 2017).

Treatment of Seizures:-Seizuresare common during the course of bacterial meningitis. Immediate therapy for seizures includes intravenous diazepam (0.1- 0.2 mg/kg/dose) or lorazepam (0.05-0.10 mg/kg/dose), and careful attention paid to the risk of respiratory suppression. Serum glucose, calcium, and sodium levels should be monitored (Tunkel, 2004). After immediate management of seizures, patients should receive phenytoin (15-20 mg/ kg loading dose, 5 mg/kg/24 hr maintenance) to reduce the likelihood of recurrence. Phenytoin is preferred to phenobarbital because it produces less CNS depression and permits assessment of a patient's level of consciousness. Serum phenytoin levels should be monitored to maintain them in the therapeutic range (10-20 µg/mL) (van de Beek, 2012).

Complications & Sequelae: During the treatment of meningitis, acute CNS complications can include seizures, increased ICP, cranial nerve palsies, stroke,cerebral or cerebellar herniation, and thrombosis of the dural venous sinuses (Wallace, 2013). Collections of fluid in the subdural space develop in 10-30% of patients with meningitis and are asymptomatic in 85-90% of patients.

Subdural effusions: are especially common in infants. Symptomatic subdural effusions may result in a bulging fontanel, diastasis of sutures, enlarging head circumference, emesis, seizures, fever, and abnormal results of cranial transillumination. CT or MRI scanning confirms the presence of a subdural effusion (Bari, 2016). In the presence of increased ICP or a depressed level of consciousness, symptomatic subdural effusion should be treated by aspiration through the open fontanel. Fever alone is not an indication for aspiration (Bari, 2016).

Cerebral infarction: Has been noted on CT scans within 1 day of onset of fever. Acute or delayed spinal cord infarction may result in quadriplegia or respiratory arrest. Brain abscess as a complication is an extremely unusual event. If an abscess is found a search for infections at other locations (such as endocarditis) should be done (Silvia, 2005).

Siadh:- occurs in some patients with meningitis, resulting in hyponatremia and reduced serum osmolality. This may exacerbate cerebral edema or result in hyponatremic seizures (Roine, 2008). Fever associated with bacterial meningitis usually resolves within 5-7 days of the onset of therapy.

Prolonged fever (>10 days) is noted in approximately 10% of patients. Prolonged fever is usually caused by intercurrent viral infection, nosocomial or secondary bacterial infection, thrombophlebitis, or drug reaction. Secondary fever refers to the recrudescence of elevated temperature after an afebrile interval, Nosocomial infections or brain abscess are especially important to consider in the evaluation of these patients. Pericarditis or arthritis may occur in patients being treated for meningitis, especially that caused by N. meningitidis. Involvement of these sites may result either from bacterial dissemination or from immune complex deposition. In general, infectious pericarditis or arthritis occurs earlier in the course of treatment than does immune-mediated disease.[35] Thrombocytosis, eosinophilia, and anemia may develop during therapy for meningitis. Anemia may be a result of hemolysis or bone marrow suppression. Disseminated intravascular coagulation is most often associated with the rapidly progressive pattern of presentation and is noted most commonly in patients with shock and purpura. The combination of endotoxemia and severe hypotension initiates the coagulation cascade; the coexistence of ongoing thrombosis may produce symmetric peripheral gangrene.[9] Long-term sequelae of meningitis result from direct inflammatory destruction of brain cells, vascular injuries, or secondary gliosis. Focal motor and sensory deficits, visual impairment, hearing loss, seizures, hydrocephalus, and a variety of cranial nerve deficits can result from meningitis.[36] Epilepsy occurs in up to 30% of children with bacterial meningitis. Seizures tend to be most common in neonates and less common in older children. Persistent focal seizures or focal seizures associated with focal neurologic deficits strongly suggest subdural effusion, abscess, or vascular lesions such as arterial infarct, cortical venous infarcts, or dural sinus thrombosis (Ginsberg, 2004).

Because generalized seizures in a metabolically compromised child may have severe sequelae, early recognition and therapy are critical; some practitioners prefer phenytoin for acute management because it is less sedating than Phenobarbital (Anderson, 2004). Sensorineural hearing loss is due to labrinthitis after cochlear infection and occur in as many as 30% of patients with pneumococcal meningitis, 10% with meningococcal, and 5-20% of those with Hib meningitis. Generally it is not related to the severity of illness. In one study, a markedly depressed CSF-to-blood glucose ratio, seizures before admission, duration of fever after initiation of therapy, and treatment with oral antibiotics before establishment of diagnosis all were associated with increased risk of deafness occurring (De Barros, 2014). Children presenting with ataxia are at high risk for having hearing loss, because vestibular and auditory branches of the eighth cranial nerve may be affected simultaneously. Hearing evaluations with evoked response audiometry, or pure-tone audiometry in older children, should be performed before or soon after hospital discharge in all children with bacterial meningitis. Recent studies have suggested that early addition of dexamethasone to the antibiotic regimen may modestly decrease the risk of hearing loss in some children with bacterial meningitis (Feigin, 2004). In addition to the variety of disorders mentioned earlier in this section, some patients with meningitis have mental retardation and severe behavioral disorders that limit their function at school and later performance in life (Ginsberg, 2004).

Prognosis:-Appropriate antibiotic therapy and supportive care have reduced the mortality of bacterial meningitis after the neonatal period to <10%. The highest mortality rates are observed with pneumococcal meningitis (Køster-Rasmussen, 2008). Coma, raised ICP, status epilepticus, shock and respiratory depression are important predictors of mortality and morbidity (Kumar et al., 2014). Severe neuro developmental sequelae may occur in 10-20% of patients recovering from bacterial meningitis, and as many as 50% have some, albeit subtle, neurobehavioral morbidity. The prognosis is poorest among infants younger than 6 mo and in those with high concentrations of bacteria/bacterial products in their CSF (Kumar et al., 2014).

Those with seizures occurring more than 4 days into therapy or with coma or focal neurologic signs on presentation have an increased risk of long-term sequelae. There does not appear to be a correlation between duration of symptoms before diagnosis of meningitis and outcome (Klinger, 2000).

Prevention:-Vaccination and antibiotic prophylaxis of susceptible at-risk contacts represent the 2 available means of reducing the likelihood of bacterial meningitis (Lowther, 2012). The availability and application of each of these approaches depend on the specific infecting bacteria.[41]

Neisseria meningitides: Chemoprophylaxis is recommended for all close contacts of patients with meningococcal meningitis regardless of age or immunization status. Close contacts should be treated with rifampin 10 mg/kg/dose every 12 hr (maximum dose of 600 mg) for 2 days as soon as possible after identification of a case of suspected meningococcal meningitis or sepsis. Close contacts include household, daycare center, and nursery school contacts, and healthcare workers who have direct exposure to oral secretions (mouth-to-mouth resuscitation, suctioning, intubation).[42] Exposed contacts should be treated immediately on suspicion ofinfection in the index patient; bacteriologic confirmation of infection should not be addition, all contacts should be educated about the early signs of meningococcal disease and the need to seek prompt medical attention if these signs develop.[42] Two quadrivalent (A, C, Y, W-135), conjugated vaccines (MCV-4; Menactra and Menveo) are licensed by the FDA. The Advisory Committee on Immunization Practices (ACIP) to the CDC recommends routine administration of this vaccine to 11-12 yr old adolescents (McIntyre, 2012).

Menactra is licensed for use in infants older than 9 mo of age, and Menveo for use in children older than 2 yr of age. There is also a bivalent meningococcal polysaccharide protein conjugate vaccine that provides protection against serogroups C and Y along with H. influenza type b. This vaccine is licensed for use in children ages 6 wk through 18 mo. High-risk patients include those with anatomic or functional asplenia or deficiencies of terminal complement proteins. Use of meningococcal vaccine should be considered for college freshmen, especially those who live in dormitories, because of an observed increased risk of invasive meningococcal infections compared to the risk in non–college-attending, age-matched controls (McIntyre, 2012).

Haemophilusinfluenzae Type B: Rifampin prophylaxis should be given to all household contacts of patients with invasive disease caused by H. influenzaetype b, if any close family member younger than 48 mo has not been fully immunized or if an immunocompromised person, of any age, resides in the household. A household contact is one who lives in the residence of the index case or who has spent a minimum of 4 hr with the index case for at least 5 of the 7 days preceding the patient's hospitalization. Family members should receive rifampin prophylaxis immediately after the diagnosis is suspected in the index case because >50% of secondary family cases occur in the 1st wk after the index patient has been hospitalized (Lowther, 2009) The dose of rifampin is 20 mg/kg/24 hr (maximum dose of 600 mg) given once each day for 4 days. Rifampin colors the urine and perspiration red-orange, stains contact lenses, and reduces the serum concentrations of some drugs, including oral contraceptives.

Rifampin is contraindicated during pregnancy (Lowther, 2009). The most striking advance in the prevention of childhood bacterial meningitis followed the development and licensure of conjugated vaccines against H. influenzaetype b. Three conjugate vaccines are licensed in the United States. Although each vaccine elicits different profiles of antibody response in infants immunized at 2-6 mo of age, all result in protective levels of antibody with an efficacy rate against invasive infections after primary series at 93%. Efficacy is not as consistent in Native American populations, a group recognized as having an especially high incidence of disease. All children should be immunized with H. influenzaetype b conjugate vaccine beginning at 2mo of age (O'Leary, 2017).

Streptococcus pneumonia: Routine administration of conjugate vaccine against S. pneumoniae is recommended for children younger than 5 yr of age. The initial dose is given at about 2 mo of age. Children who are at high risk of invasive pneumococcal infections, including those with functional or anatomic asplenia and those with underlying immunodeficiency (such as infection with HIV, primary immunodeficiency, and those receiving immunosuppressive therapy) should also receive the vaccine (Centers for Disease Control and Prevention, 2013).

Aim of study

- Early detection of possible post-meningitis complications.
- To find the possible prognostic factors to identify high risk complications.

Patient and method: We conducted a study during the period of 1 year from january/2017 to January/2018 in the infectious follow up clinic in the Central Teaching Hospital of Pediatrics to identify the early complications of meningitis. Out of 668 patients admitted in the central child teaching hospital\infectious ward were confirmed bacterial meningitis, 123 patients were selected for follow up after discharge from hospital for 12 months and consent was taken from parents, after applying exclusion criteria 8 were excluded, which making total no. of studied patients is 115.

Inclusion criteria

- Age group above 1 month and below 15 years
- Confirmed acute meningitis by CSF culture, &/or by CSF findings (as mentioned in table1 page8), or by blood culture with clinical features of meningitis.
- informed consent from parents for follow up

Exclusion criteria

- Age group below 1 month or above 15 years old
- Rejection of parents to follow up or incompliance with follow up visits
- Presence of shunt within the central nervous system for hydrocephalus.
- Presence of a chronic neurologic disease (e.g. cerebral palsy, epilepsy, etc.).

We obtained the following data from all cases: Name, age, sex, date of admission, history of antibiotics use and its duration, signs and symptoms at presentation suggestive of complications (impaired level of consciousness/coma, prolonged seizure >3 days, history of symptoms for more than

48 hours without treatment, and focal neurological deficit), all of them sent for investigations (blood for WBC count, CRP, blood urea, serum electrolyte, and blood culture; CSF for glucose, protein level, total WBC count and differential and culture, EEG, and brain CT scan done for high risk patients, and MRI if needed). We depend on CSF findings including CSF glucose which considered low when it was <40mg/dl, CSF protein which considered high when it was >100mg/dl (0.45mmol/dl), CSF WBC count (neutrophil) which considered predominate when it was >50% of total WBC count in CSF.[16] Partially treated meningitis was considered if there is a history of antibiotics use before LP, negative CSF culture, negative gram stain and CSF pleocytosis (CSF WBC>5/mm^3) with neutrophil predominance, and CSF protein normal or slightly elevated.[16] Follow up in infectious clinic in central teaching hospital of pediatrics was carried out for 12 months after discharge to all patients as follows:

Follow up visits weekly for 1 month, then every 2 weeks for 2 months, then monthly for 3 months. Patients were examined in each visit for the following: General examination, growth parameters (weight, height, and head circumference), developmental assessment, hearing assessment by audiologist and visual assessment by ophthalmologist, any history of fit or neurological deficits, sent follow up miscellaneous investigations according to the conditions of patients, sending EEG after a period of 4-6months of anti-epileptic treatment, repeating EEG after continuing further 4-6months for patients in which their EEG was still abnormal, or in case normal EEG results then patients undergo scientific gradual tapering schedule, also sending CT scan and MRI of brain as needed.

RESULTS

Among 115 cases studied there were 55 patients that developed early complications, details are as follows:

- Benign course patients (patients who developed no complications after meningitis) were 60 in number which account for 52.2%
- Complicated course patients were 55 in number, which account for 47.8%.

Complicated cases had one or more of the following complications: Convulsions (epilepsy) 26 (47.3%), developmental delay 8 (14.5%), hearing defect 6 (10.9%), cerebral palsy 4(7.3%), hydrocephalus 3(5.5%), vision abnormalities 2 (3.6%), recurrent meningitis 2 (3.6%), focal neurological deficits 2(3.6%), behavioral 2 (3.6 %) One of cases of recurrent meningitis died during illness. The following table shows the no. and percentage of each benign and complicated cases according to both age group and gender difference, which reveals a great significance in age group below 6 months, while there is no significant difference according to gender. Some of patients were diagnosed other than meningitis in other medical institutes and then diagnosed as meningitis in our hospital, some of them were already receiving antibiotics, but not in a meningitic dose. CSF gram stain was not included in our study because of the lack of laboratory equipment needed to perform this study in our hospital.

Statistical analysis: Analysis of data was carried out using the available statistical package of SPSS-24 (Statistical Packages for Social Sciences- version 24). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values). The significance of difference of different percentages (qualitative data) were tested using Pearson Chi-square test (χ^2-test) with application of Yate's correction or Fisher Exact test whenever applicable. Statistical significance was considered whenever the P value was equal or less than 0.05.

DISCUSSION

In spite of the great progress of medicine, acute bacterial meningitis still causes considerable morbidity and mortality in children in developed countries (de Jonge, 2010; Koomen, 2003) and developing countries (Molyneux, 2006; Antoniuk, 2011). Sensorineural hearing loss, vision abnormalities, seizures, and mental retardation, as well as more subtle outcomes, such as cognitive, academic and behavioral, are seen in post-meningitis children (Anderson et al., 2004). Chandran et al. (2011), in their research literature, they reported that 49% of the survivors of childhood bacterial meningitis had one or more sequelae sooner or later. Most of those were related to behavioral and/or academic disorders (45%). In this study it was found that 55 cases (47.8%) of those studied subjects had one or more complications, most of which were seizures (epilepsy) 26 cases (47.3%), followed by developmental delay 8 cases (14.5%).

The reason that there is a difference in the most common complication is that more time was needed to detect behavioral and/or academic limitations as when the child starts to socially interact and enter school, this study focused on the occurrence of early sequelae of meningitis that can be detected during the first year after diagnosis. Anticipators of early neurological complications are crucially important, since they are the first signs in predicting, and possible prevention, of the long-term complications of childhood bacterial meningitis. Several studies of the clinical picture and prognostic factors in children with bacterial meningitis had been conducted (de Jonge, 2010; Antoniuk, 2011; Grimwood, 2000). Most of studies were conducted in developed countries. In this study, we prospectively analyzed the influence of 13 prognostic factors potentially important for neurological complications in children with bacterial meningitis in a country with limited resources. young age group (indicated as below of 12 months) is considered an important risk factor for poor outcome in children with meningitis in this thesis, also, the lower age at 6 months had been identified as a predictor of sequelae. This agrees with Namani S. et al. who detected significance of young age below 12months as risk factor for future sequelae (Namani, 2013). If compared to older children and adults, babies below 12 months are particularly vulnerable to complications because their body immune system is still progressing to develop 'not yet fully developed'. And when babies get infected and develop the disease, they are more difficult to cope with or diagnose early. Gender is found to be not significant as a risk factor for sequelae, with approximately equal percentage of complications in males and females (58% for male, 41% for female), and this goes along previous article done by dash. et al. and Namani et al.(2005) (Namani, 2013). but it contradict with a study by Johansson et al. in which revealed an important sex-related differences were found that might explain the higher case fatality rates for boys than girls (Johansson Kostenniemi et al., 2015). But this study is lacking sufficient details about the complications and sequelae and their association with gender.

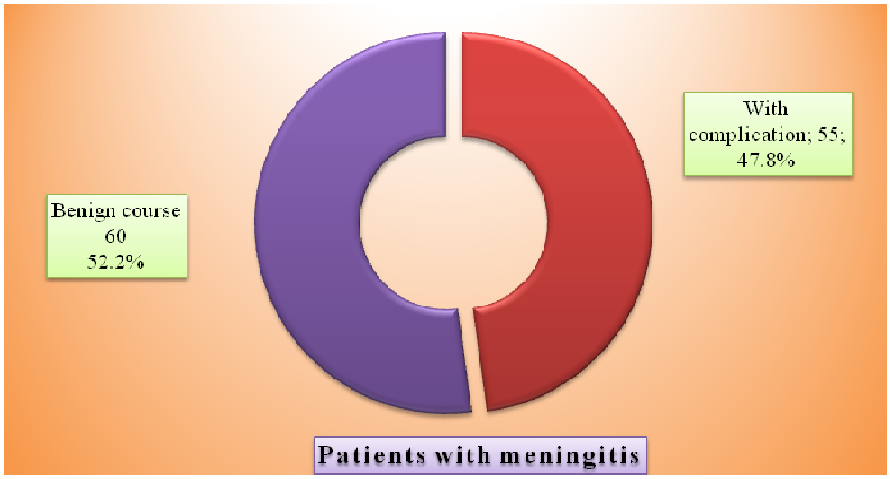

Figure 1. Showing the number and percentage of confirmed bacterial meningitis and the complicated cases.

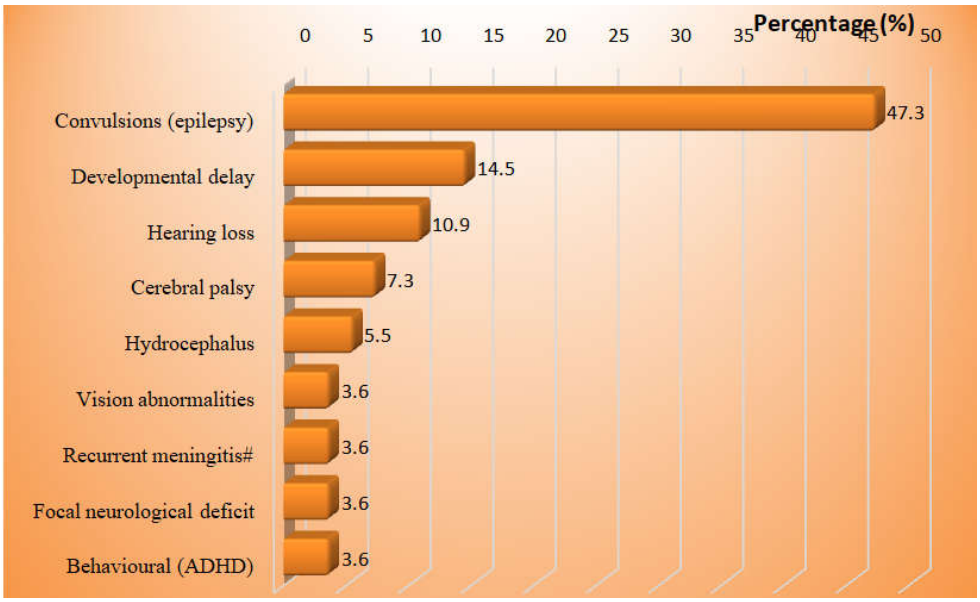

Figure 2. Types of sequelae of meningitis and percentage of each one to the total complicated cases

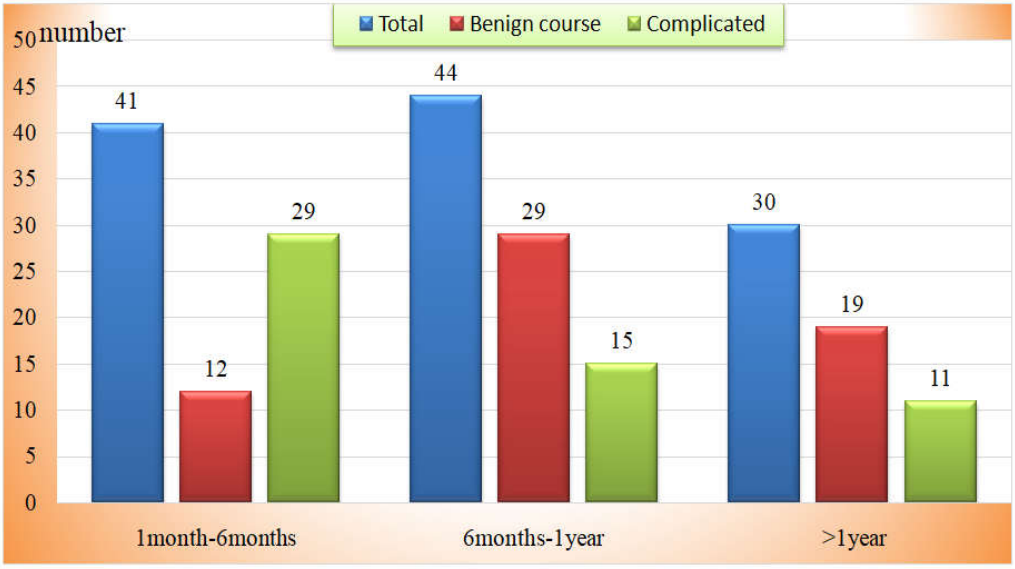

Figure 3. Of complicated cases according to the age group

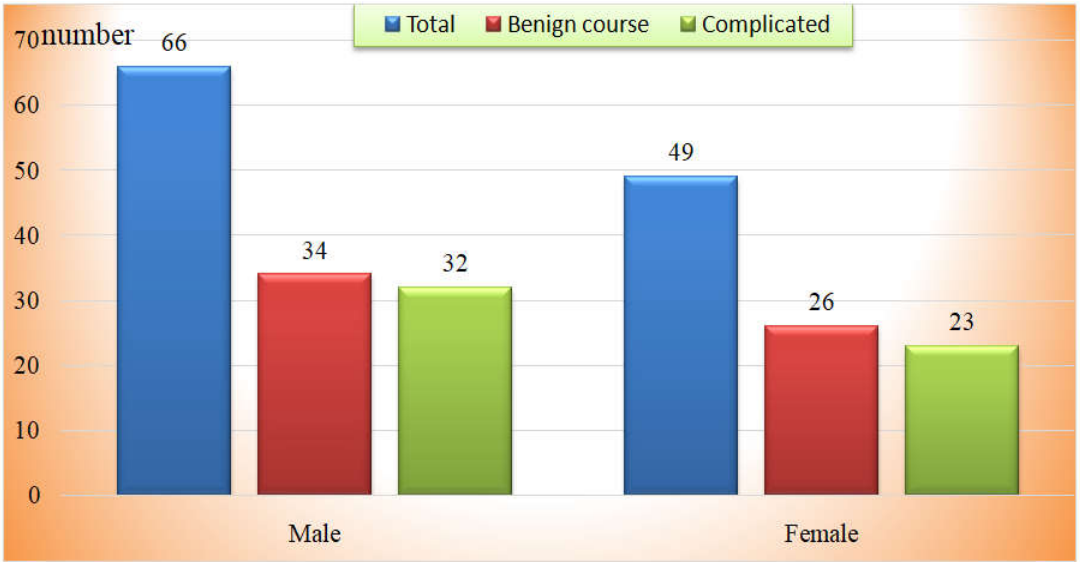

Figure 4. Of complicated cases according to gender

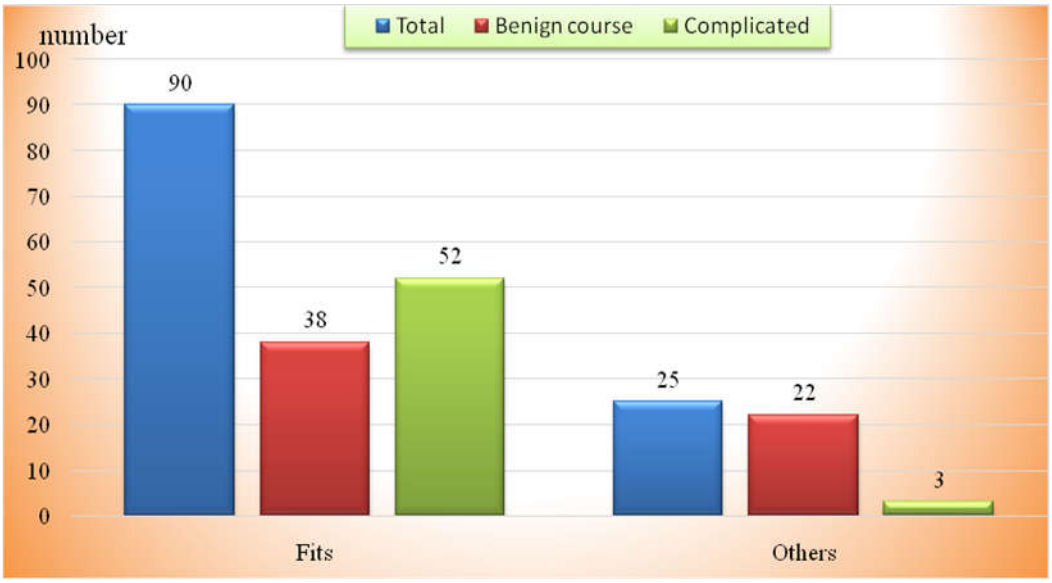

Figure 5. Of complicated cases according to presentation

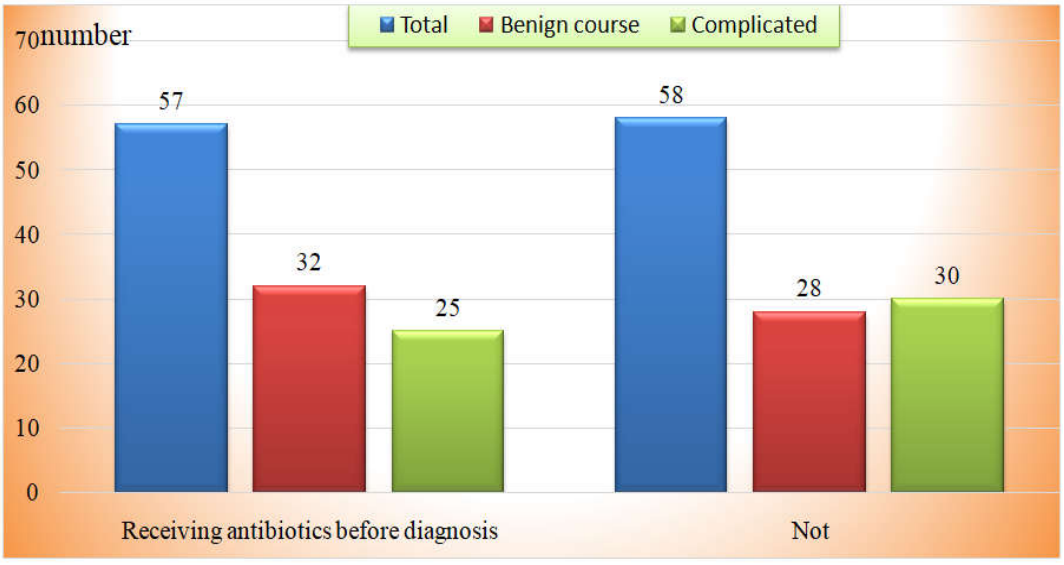

Figure 6. Of complicated cases in patients who received antibiotics prior to diagnosis and in those who didn't receive antibiotics

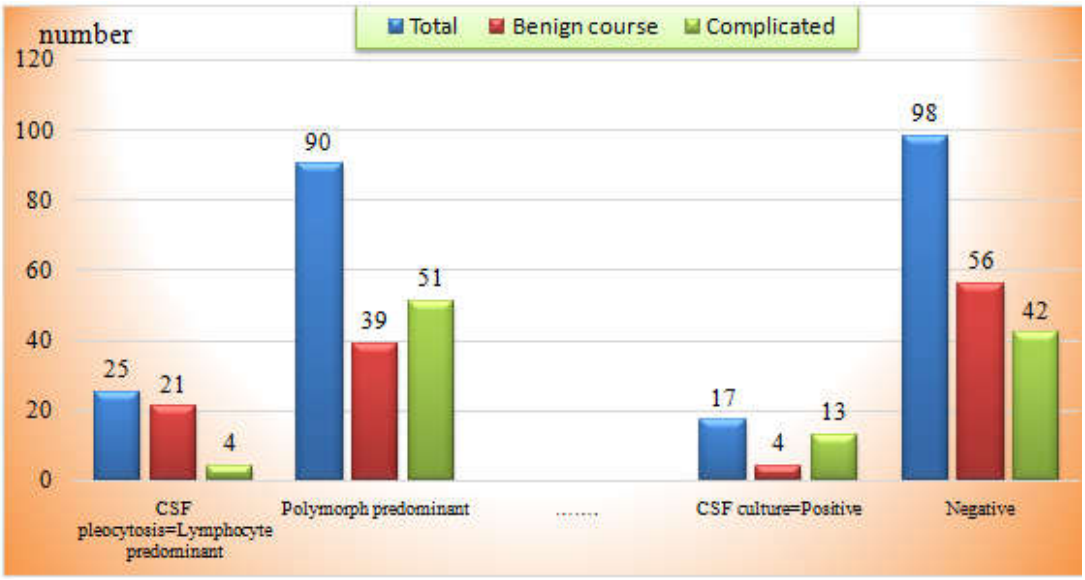

Figure 7. No of complicated cases in relation to results of CSF pleocytosis and CSF culture

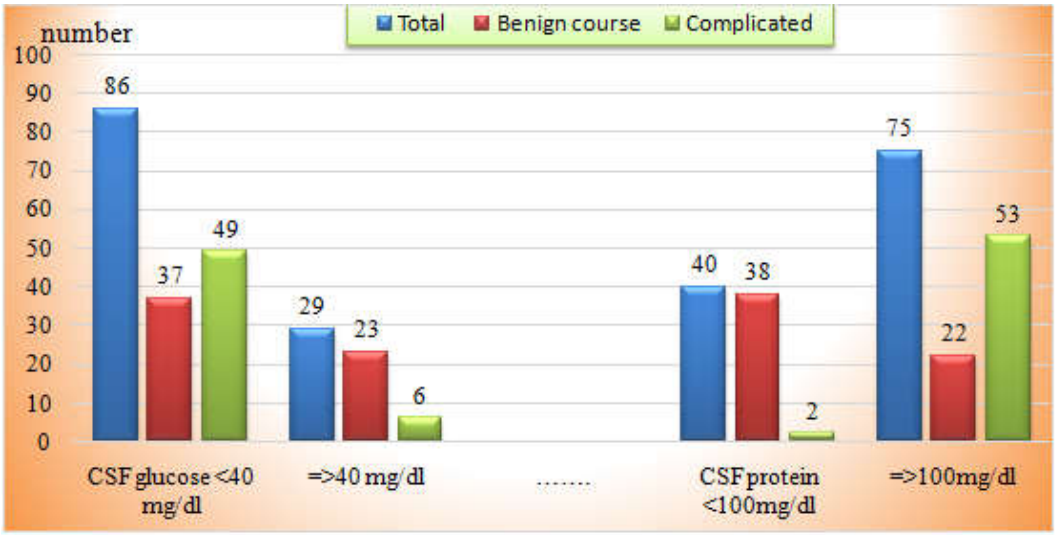

Figure 8. Of complicated cases in relation to CSF analysis results (sugar, protein)

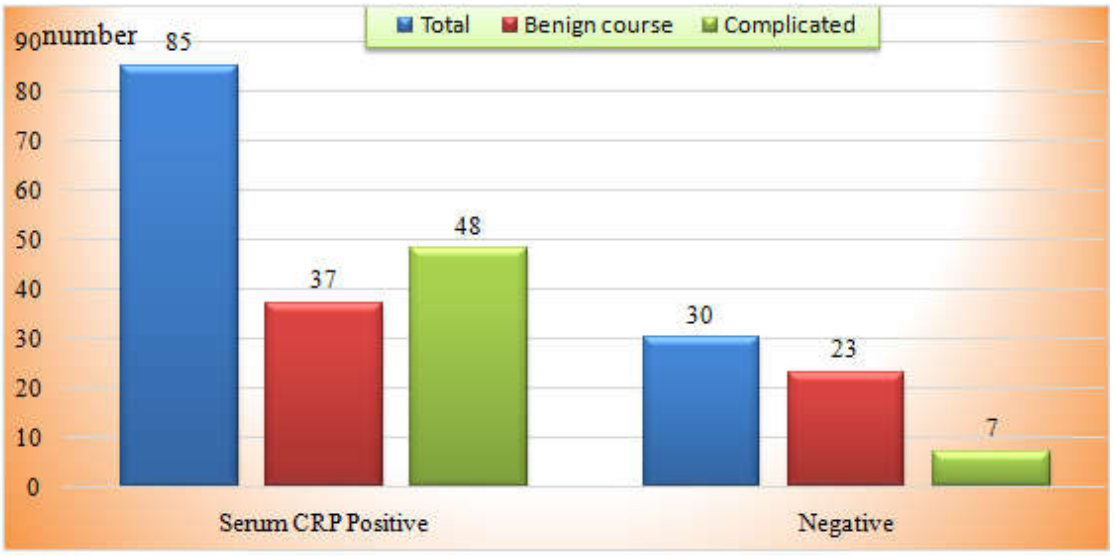

Figure 9. No. of complicated cases according to serum CRP results

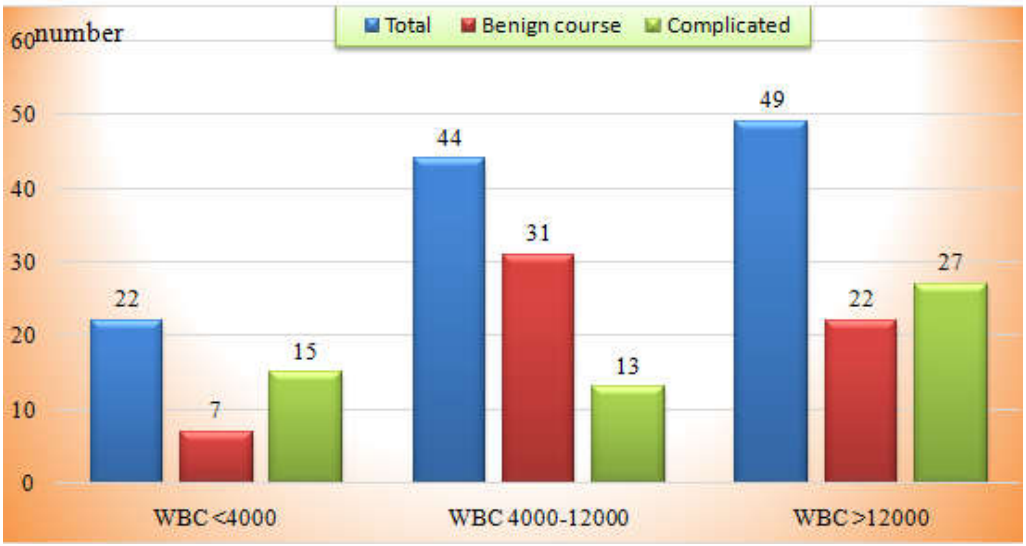

Figure 10: no. of complicated cases according to serum WBC count results

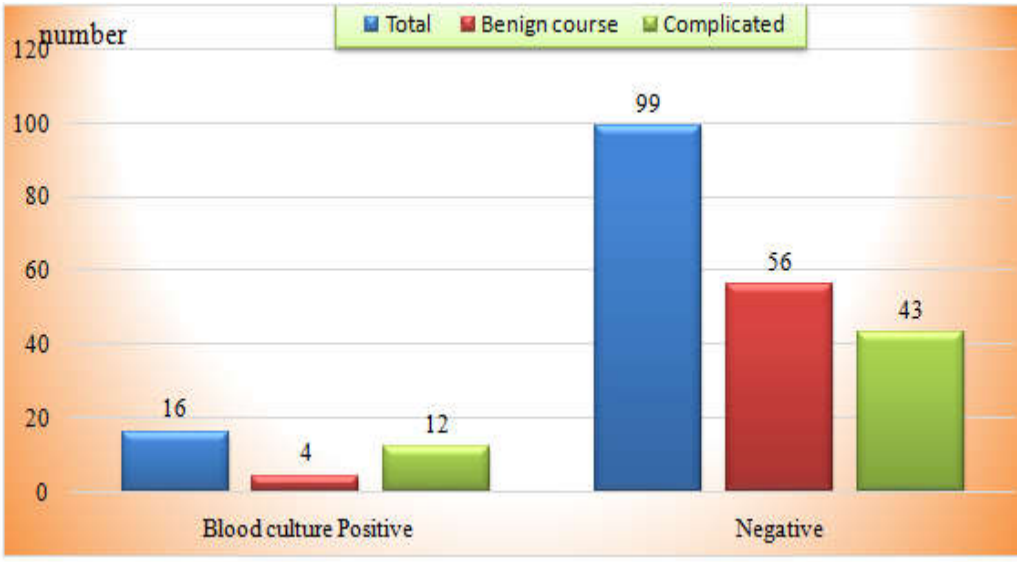

Figure 11: no. of complicated cases in relation to results of blood culture

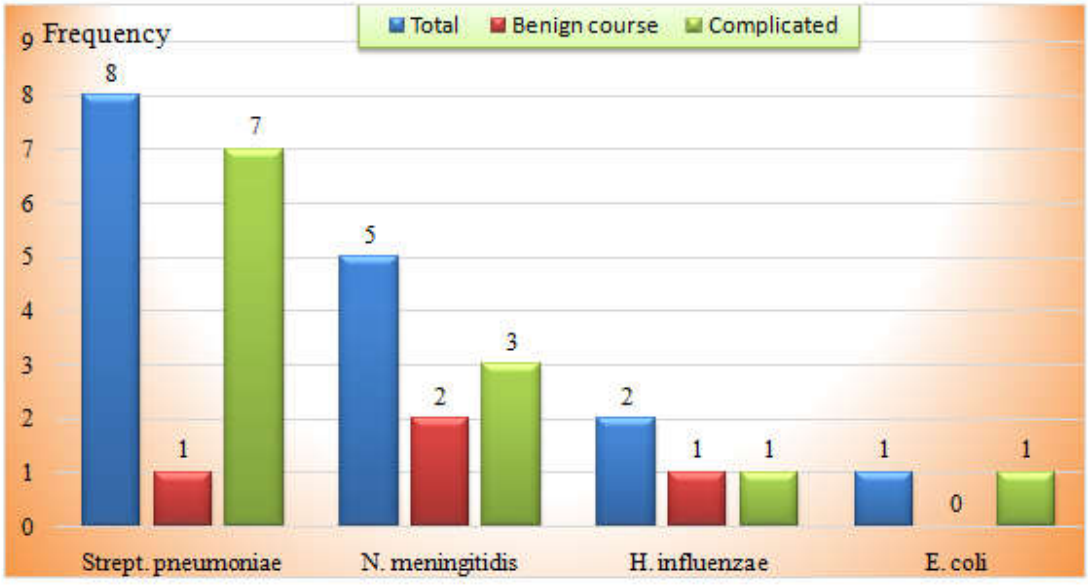

Figure 12: no. of complicated cases in relation to blood culture specific microorganisms

Table 1. Showing types of meningitis by etiology and csf findings:[8]

Types of meningitis	Cerebrospinal fluid appearance	Cell count	Polymorphonuclear cells	Lymphocytes	Protein (mg/dl)	glucose
Bacterial	cloudy	Few 100 to > 1000	+++	+	Raised 100 to >500	↓↓
Partially treated	clear	5-few 100	++	+	Raised 100-500	↓
tubercular	clear	<500	-	+++	Raised 100-500	↓
viral	clear	10-500	+	++	N (<50) or raised up to 100	N

Table 2. Antibiotic treatment modalities in different age groups:[29]

Drugs		Neonates	Infants and children
	0-7 days	8-28 days	
Amikacin	15-20mg divided q12h	30mg divided q8hr	20-30mg divided q8hr
Ampicillin	150mg divided q8h	200mg divided q6hr or q8hr	300mg divided q6hr
Cefotaxime	100-150mg divided q8h or q12h	150-200mg divided q6hr or q8hr	225-300mg divided q6hr or q8hr
Ceftriaxone	------	------	100mg divided q12hr or q24hr
Ceftazidime	100-150mg divided q8h or q12h	150mg divided q8hr	150mg divided q8hr
Gentamicin	5mg divided q12h	7.5mg divided q8hr	7.5mg divided q8hr
Meropenem	-------	-----	120mg divided q8hr
Nafcillin	75mg divided q8hr or q12hr	100-150mg divided q6hr or q8hr	200mg divided q6hr
Penicillin G	150,000units divided q8hr or q12hr	200,000units divided q6hr or q8hr	300,000units divided q4hr or q6hr
Rifampin	-------	10-20mg divided q12hr	10-20mg divided q12hr or q24hr
Tobramycin	5mg divided q12hr	7.5mg divided q8hr	7.5mg divided q8hr
vancomycin	20-30mg divided q8hr or q12hr	30-45mg divided q6hr or q8hr	60mg divided q6hr

Table 3. Showing list of the common sequelae after acute bacterial meningitis:[2]

Late onset seizures
Subdural empyema
Infarcts, cerebritis and brain abscess
Hydrocephalus
Cranial nerve involvement
Sensorineural deafness
Diabetes insipidus
Spread of infections to distant sites (pneumonia, pericarditis, arthritis, and osteomyelitis)

Table 4. Impact of age and sex distribution on sequelae of bacterial meningitis

	Total		Benign course		Complicated		P value
	No	%	No	%	No	%	
Presentation at diagnosis							
Fits#	90	78.3	38	63.3	52	94.5	0.0001*
Other than fit (fever, vomiting, headache)	25	21.7	22	36.7	3	5.5	
# prolonged seizures (more than 72 hours)	5		2		3		
*Significant difference between percentages using Pearson Chi-square test at 0.05 level							

(P-value of age highly significant using Pearson Chi-square test at 0.05 level of significance, whilep-value of sex not significant using Pearson Chi-square test at 0.05 level of significance)

Table 5. Impact of clinical presentation and on sequelae of acute bacterial meningitis

	Total		Benign course		Complicated		P value
	No	%	No	%	No	%	
Presentation at diagnosis							
Fits#	90	78.3	38	63.3	52	94.5	0.0001*
Other than fit (fever, vomiting, headache)	25	21.7	22	36.7	3	5.5	
# prolonged seizures (more than 72 hours)	5		2		3		
*Significant difference between percentages using Pearson Chi-square test at 0.05 level							

Table 6. Impact of history of receiving antibiotics prior to diagnosis on sequelae of acute bacterial meningitis

Receiving antibiotics before diagnosis	total	%	benign	%	complicated	%	p value
Yes	57	49.6	32	53.3	25	45.5	0.511
No	58	50.4	28	46.7	30	54.5	

Table 7: Impact of CSF laboratory findings on the sequelae of bacterial meningitis

	Total		Benign course		Complicated		P value
	No	%	No	%	No	%	
CSF pleocytosis							
Lymphocyte predominant	25	21.7	21	35.0	4	7.3	0.0008*
Polymorph predominant	90	78.3	39	65.0	51	92.7	
CSF glucose							
<40 mg/dl (2.2mmol/L)	86	74.8	37	61.7	49	89.1	0.002*
=>40 mg/dl (2.2mmol/L)	29	25.2	23	38.3	6	10.9	
CSF protein							
<100mg/dl	40	34.8	38	63.3	2	3.6	0.0001*
=>100mg/dl	75	65.2	22	36.7	53	96.4	
CSF culture							
Positive	17	14.8	4	6.7	13	23.6	0.022*
Negative	98	85.2	56	93.3	42	76.4	

*Significant difference between percentages using Pearson Chi-square test at 0.05 level

CSF gram stain was not included in our study because of the lack of laboratory equipment needed to perform this study in our hospital.

Table 8. Impact of serum laboratory findings on incidence of sequelae of meningitis

	Total		Benign course		Complicated		P value
	No	%	No	%	No	%	
Serum CRP							
Positive(titer >2folds)	85	73.9	37	61.7	48	87.3	0.004*
Negative	30	26.1	23	38.3	7	12.7	
WBC count							
<4000	22	19.1	7	11.7	15	27.2	0.01*
4000 -12000	44	38.3	31	51.7	13	23.7	
>12000	49	42.6	22	36.7	27	49.1	

*Significant difference between percentages using Pearson Chi-square test at 0.05 level

The severity of the clinical presentation, described as occurrence of prolonged seizures at presentation, is identified as the most common prognostic factor strongly predictor for neurological complications in this study, as indicated in numerous studies in developed countries (Oostenbrink, 2002) and developing countries (Antoniuk et al., 2011). Klinger et al. found that the duration of seizures more than 72 hours and the presence of coma were the predictors of adverse outcome, as well as in our study in which there is a great prevalence of sequelae in patients with prolonged seizures more than 72 hours (Klinger, 2000) History of receiving antibiotics more than 2 days before admission and diagnosis of meningitis was found to be not significant in predicting early sequelae, this comes along with Namani SA et al. (2013) Many clinical trials have been conducted to determine the risk factors in variations of CSF different parameters (Nigrovic, 2009; Antoniuk, 2011), this study detected a great risk factors when CSF pleocytosis is neutrophil predominant, CSF protein when > 100mg/dl, and CSF glucose is < 40mg/dl, as factors to predict neurological complications of bacterial meningitis in children, this is also strongly confirmed by many trials such as Namani et al. and Xu et al. and others.[53][57] Positive CSF culture also carries a great significance in predicting post-meningitis sequelae according to this study, this is also suggested by Bari et al. and Hailemeskel et al.[35][58] Serum laboratory findings were also studied to know their significance in this study; we found that high titer serum C-reactive protein (2folds normal) was a risk factor associated with complications, Singh et al. found the same results in their study.[58] Leukopenia (WBC count less than 4000)is considered important as a risk factor of unfavorable outcome, a study by klinger g identified leukopenia(below 4000) was the most important predictor of adverse outcome, and de Jonge et al. mentioned the importance of WBC count to detect meningitis complications[45] The literature suggests an association between meningitis by S. pneumoniae and unfavorable evolution.

According to Antoniuk et al., S. pneumoniae infection was considered a risk factor for meningitis complications.[48] In this study, complications disorders have developed more frequently in patients infected with S. pneumoniae.

Conclusion

In conclusion, the age of less than 12 months and the severity of clinical presentation on admission (occurrence of seizures especially prolonged), as well as multiple CSF and serum laboratory findings were identified as the strongest predictors of neurological complications and may have value in selecting patients for a treatment.

Recommendations

- This thesis illustrates the importance of implementing protocols for early prediction and treatment of early sequelae of bacterial meningitis to reduce the morbidity and the incidence of neurological complications is the goal of our future treatments in children.
- We recommend improving laboratory work especially in examining the CSF analysis, culture and gram stain, and PCR because we are dealing with serious problem in which there are high rates of mortality and morbidity.
- Careful follow-up for months or years is needed for all patients in order to be certain about the outcome, giving prophylaxis or treatment to reduce the impact of sequelae, and to provide the proper rehabilitation for those who need it.
- Prevention of the disease by chemoprophylaxis to contacts and for high risk children is also of great attention, Routine use of conjugated vaccines could provide substantial health and economic benefits through the prevention of childhood meningitis cases, deaths and disability.

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