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Infection of the central nervous system (CNS)

It's the most common cause of fever associated with signs and symptoms of CNS disease in children.

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; regardless of etiology, most patients with CNS infection have similar clinical manifestations.

Infection of the CNS may be diffuse or focal. Meningitis and encephalitis are examples of diffuse infection. 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. Brain abscess is the best example of a focal infection of the CNS.

Acute Bacterial Meningitis beyond the Neonatal Period

Bacterial meningitis is one of the most potentially serious infections occurring in infants and older children.

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 *Haemophilus influenzae* 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.

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. The mode of transmission is probably person-to-person contact through respiratory tract secretions or droplets.

Defects of the complement system (C5-C8) are associated with recurrent meningococcal infection, and defects of the properdin system are associated with a significant risk of lethal meningococcal disease.

A congenital or acquired CSF leak across a mucocutaneous barrier, such as a lumbar dural sinus, or CSF leakage through a rupture of the

meninges as a result of a basal skull fracture, is associated with an increased risk of pneumococcal meningitis.

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 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. *Cerebral infarction*, resulting from vascular occlusion because of inflammation, vasospasm, and thrombosis, is a frequent sequela. 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 ICP** is a result of cell death (cytotoxic cerebral edema), cytokine-induced increased capillary vascular permeability (vasogenic cerebral edema), and, possibly, increased hydrostatic pressure (interstitial cerebral edema) after obstructed reabsorption of CSF in the arachnoid villus or obstruction of the flow of fluid from the ventricles. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) may produce excessive water retention and potentially increase the risk of elevated ICP.

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. **Raised CSF** protein levels are partly a result of increased vascular permeability of the blood–brain barrier and the loss of albumin-rich fluid from the capillaries and veins traversing the subdural space. Continued transudation may result in subdural effusions, usually found in the later phase of acute bacterial meningitis. **Hypoglycorrhachia** (reduced CSF glucose levels) is attributable to decreased glucose transport by the cerebral tissue.

Clinical features

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, or an erythematous macular rash.

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. Increased ICP is suggested by headache, emesis, bulging fontanel or diastasis (widening) of the sutures, oculomotor (anisocoria, ptosis) or abducens 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.

Cranial neuropathies of the ocular, oculomotor, abducens, 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.

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.

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.

Additional manifestations of meningitis include **photophobia**.

Diagnosis

The diagnosis of acute pyogenic meningitis is confirmed by analysis of the CSF, which typically reveals microorganisms on Gram stain and culture, a neutrophilic pleocytosis, elevated protein, and reduced glucose concentrations. LP should be performed when bacterial meningitis is suspected. Contraindications for an mimmediate LP include (1) 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 (2) severe cardiopulmonary compromise requiring prompt resuscitative measures for shock or in patients in whom positioning for the LP would further compromise cardiopulmonary function; and (3) infection of the skin overlying the site of the LP. Thrombocytopenia is a relative contraindication for LP.

LP may be performed after increased ICP has been treated or a brain abscess has been excluded. Normal healthy neonates may have as many as 30 leukocytes/mm3 (usually <10), but older children without viral or bacterial meningitis have <5 leukocytes/mm3 in the CSF; in both age groups there is a predominance of lymphocytes or monocytes. Pleocytosis with a lymphocyte predominance may be present during the early stage of acute bacterial meningitis; conversely, neutrophilic pleocytosis may be present in patients in the early stages of acute viral meningitis. **The Gram stain** is positive in 70-90% of patients with untreated bacterial meningitis. **Latex agglutination** : Helpful in partially treated meningitis

Specific but not that sensitive Strep pneumo – 96% specific, 70 -100 % sensitive.

PCRs are available for neisseria and pneumococcus

Both are sensitive and specific , DNA load correlates with mortality for Neisseria.

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.

Peripheral WBC, CSF lactate, procalcitonin, and various cytokines are used to differentiate bacterial (usually elevated) from viral causes of meningitis.

TREATMENT

The therapeutic approach to patients with presumed bacterial meningitis depends on the nature of the initial manifestations of the illness.

A child with 1)rapidly progressing disease of less than 24 hr duration, or 2) have a more protracted subacute course and become ill over a 4-7 day period; in the absence of increased ICP, should receive antibiotics as soon as possible after an LP is performed. If there are signs of increased ICP or focal neurologic findings, antibiotics should be given without

performing an LP and before obtaining a CT scan. Increased ICP should be treated simultaneously.

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. pneumonia*** . In the United States, 25-50% of strains of *S. pneumoniae* are currently resistant to penicillin;
vancomycin (60 mg/kg/24 hr), given every 6 hr **plus** 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) for 10-14 days.

Most strains of ***N. meningitidis*** are sensitive to penicillin and cephalosporins for 5-7 days.

For ***H. influenzae*** **type b**, Approximately 30-40% of isolates of *H. influenzae* type b produce β-lactamases and, therefore, are resistant to ampicillin. These β-lactamase–producing strains are sensitive to the extended-spectrum cephalosporins.
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) for 7-10 days should also be used in initial empirical therapy.

If ***L. monocytogenes*** infection is suspected, as in young infants or those with a T-lymphocyte deficiency, ampicillin (200 mg/kg/24 hr, given every 6 hr) also should also be given because cephalosporins are inactive against L. monocytogenes.

If patient immunecompromised and Gram negative bacterial meningitis are suspected, initial therapy might include ceftazedime and an aminoglycoside ore meropenem.

Repeat examination of CSF is indicated in some neonates, in all patients with Gram-negative bacillary meningitis, or in infection caused by a β-lactam–resistant S. pneumoniae. The CSF should be sterile within 24-48 hr of initiation of appropriate antibiotic therapy.

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 may produce additional neurologic injury with worsening of CNS signs and symptoms. 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.

Supportive Care

Pulse rate, blood pressure, and respiratory rate should be monitored frequently. Neurologic assessment, including pupillary reflexes, level of consciousness, motor strength, cranial nerve signs, and evaluation for seizures, should be made frequently in the 1st 72 hr, when the risk of neurologic complications is greatest. Important laboratory studies include an assessment of blood urea nitrogen; serum sodium, chloride, potassium, and bicarbonate levels; urine output and specific gravity; complete blood and platelet counts.

Seizures are common during the course of bacterial meningitis. Immediate therapy for seizures includes intravenous diazepam (0.1- 0.2 mg/kg/dose), and careful attention paid to the risk of respiratory suppression. Serum glucose, calcium, and sodium levels should be monitored. 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.

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 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.

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.

Encephalopathy describes a diffuse brain disorder, in which two of the followings are present:
1. Altered state of consciousness, 2. Altered cognition or personality.
3. Seizures. ***Encephalitis***: encephalopathy plus CSF pleocytosis.

Viral Meningoencephalitis (ME)

Viral ME is an acute inflammatory process involving the meninges and, to a variable degree, brain tissue. These infections are relatively common and may be caused by a number of different agents. The CSF is characterized by pleocytosis and the absence of microorganisms on Gram stain and routine bacterial culture. In most instances, the infections are self-limited. In some cases, substantial morbidity and mortality occur.
Enteroviruses are the most common cause of viral ME. Several members of the **herpes family** of viruses can cause ME. Herpes simplex virus (HSV) type 1 is an important cause of severe, sporadic encephalitis in children and adults. Brain involvement usually is focal; progression to coma and death occurs in 70% of cases without antiviral therapy.
Varicella-zoster virus may cause CNS infection in close temporal relationship with chickenpox. Mumps is a common pathogen in regions where mumps vaccine is not widely used.
Mumps ME is mild, but deafness from damage of the 8th cranial nerve may be a sequela.
ME is caused occasionally by respiratory viruses (adenovirus, influenza virus, parainfluenza virus), rubeola, rubella, or rabies; it may follow live virus vaccinations against polio, measles, mumps, or rubella.
The progression and severity of disease are determined by the relative degree of meningeal and parenchymal involvement, which, in part, is determined by the specific etiology. The clinical course resulting from infection with the same pathogen varies widely.
The onset of illness is generally acute, although CNS signs and symptoms are often preceded by a nonspecific febrile illness of a few days' duration. The presenting manifestations in older children are headache and hyperesthesia, and in infants, irritability and lethargy. Headache is most often frontal or generalized. Fever, nausea and vomiting, photophobia, and pain in the neck, back, and legs are common. As body temperature increases, there may be mental dullness, progressing to stupor in combination with bizarre movements and convulsions. Focal neurologic signs may be stationary, progressive, or fluctuating. Loss of bowel and

bladder control may occur. Examination often reveals nuchal rigidity without significant localizing neurologic changes, at least at the onset.
The diagnosis of viral encephalitis is usually made on the basis of the clinical presentation of nonspecific prodrome followed by progressive CNS symptoms. The diagnosis is supported by examination of the CSF, which usually shows a mild mononuclear predominance. Other tests of potential value in the evaluation of patients with suspected viral ME include an electroencephalogram (EEG) and neuroimaging studies.
With the exception of the use of acyclovir for HSV encephalitis, treatment of viral meningoencephalitis is supportive.

Guillain-Barre Syndrome

Guillain-Barre syndrome is a postinfectious polyneuropathy involving mainly motor but sometimes also sensory and autonomic nerves. This syndrome affects people of all ages and is not hereditary.

Clinical Manifestations

The paralysis usually follows a nonspecific viral infection by about 10 days. The original infection might have caused only gastrointestinal or respiratory tract symptoms.
Weakness usually begins in the lower extremities and progressively involves the trunk, the upper limbs, and finally the bulbar muscles, a pattern known as **Landry ascending paralysis.** Proximal and distal muscles are involved relatively symmetrically, but asymmetry is found in 9% of patients. The onset is gradual and progresses over days or weeks. Particularly in cases with an abrupt onset, tenderness on palpation and pain in muscles is common in the initial stages. Affected children are irritable. Weakness can progress to inability or refusal to walk and later to flaccid tetraplegia.

Bulbar involvement occurs in about half of cases. Respiratory insufficiency can result. Dysphagia and facial weakness are often impending signs of respiratory failure. They interfere with eating and increase the risk of aspiration. The facial nerves may be involved. Some young patients exhibit symptoms of viral meningitis or meningoencephalitis. Extraocular muscle involvement is rare, but in an uncommon variant, oculomotor and other cranial neuropathies are severe

early in the course. **Miller-Fisher syndrome** consists of acute external ophthalmoplegia, ataxia, and areflexia. Papilledema is found in some cases, although visual impairment is not clinically evident. Urinary incontinence or retention of urine is a complication in about 20% of cases but is usually transient.

Tendon reflexes are lost, usually early in the course. The autonomic nervous system is also involved in some cases. Lability of blood pressure and cardiac rate, postural hypotension, episodes of profound bradycardia, and occasional asystole occur.

Laboratory Findings and Diagnosis

CSF studies are essential for diagnosis. The CSF protein is elevated to more than twice the upper limit of normal, glucose level is normal, and there is no pleocytosis. Fewer than 10 white blood cells/mm^3 are found. The results of bacterial cultures are negative, and viral cultures rarely isolate specific viruses. The dissociation between high CSF protein and a lack of cellular response in a patient with an acute or subacute polyneuropathy is diagnostic of Guillain-Barre syndrome. Motor NCVs are greatly reduced, and sensory nerve conduction time is often slow. Electromyography (EMG) shows evidence of acute denervation of muscle. Serum creatine kinase (CK) level may be mildly elevated or normal.

Treatment

Patients in early stages of this acute disease should be admitted to the hospital for observation because the ascending paralysis can rapidly involve respiratory muscles during the next 24 hr. Respiratory effort (negative inspiratory force, spirometry) must be monitored to prevent respiratory failure and respiratory arrest. Patients with slow progression might simply be observed for stabilization and spontaneous remission without treatment. Rapidly progressive ascending paralysis is treated with intravenous immunoglobulin (IVIG), administered for 5 days. Plasmapheresis and/or immunosuppressive drugs are alternatives if IVIG is ineffective. Steroids are not effective. Combined administration of immunoglobulin and interferon is effective in some patients. Supportive care, such as respiratory support, prevention of decubiti in children with

flaccid tetraplegia, and treatment of secondary bacterial infections, is important.

Prognosis

The clinical course is usually benign, and spontaneous recovery begins within 2-3 wk. Most patients regain full muscular strength, although some are left with residual weakness. The tendon reflexes are usually the last function to recover. Improvement usually follows a gradient opposite the direction of involvement: bulbar function recovering first, and lower extremity weakness resolving last. Bulbar and respiratory muscle involvement can lead to death if the syndrome is not recognized and treated. Although prognosis is generally good and the majority of children recover completely, 3 clinical features are predictive of poor outcome with sequelae: cranial nerve involvement, intubation, and maximum disability at the time of presentation.