Central nervous system infection

Lectures 1+2

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Infection of the central nervous system (CNS)

INTRODUCTION:

Infection of the central nervous system (CNS) is a significant cause of morbidity and mortality in children. Identification of CNS infections can be problematic for clinicians because symptoms can be nonspecific in younger infants, and delayed or missed diagnosis can amplify the morbidity and mortality rates associated with these diseases.

Implementation of multiple conjugate vaccines has greatly reduced the incidence of bacterial CNS infections. Nonetheless, bacterial and viral infections remain a significant cause of CNS disease.

Independent of etiology, many patients with CNS infection have similar clinical manifestations. The severity and constellation of signs are determined by host-pathogen interactions and the affected region of the CNS.

Q1/ WHAT ARE THE COMMON SYMPTOMS AND SIGNS OF CNS INFECTION?

Common symptoms include headache, nausea, vomiting, anorexia, photophobia, restlessness, altered state of consciousness, and irritability.

Common signs include fever, neck pain, nuchal rigidity, focal neurologic deficits, seizures, obtundation, and coma.

Q2/ WHAT IS THE DIFFERENCE BETWEEN MENINGITIS AND ENCEPHALITIAS?

Meningitis describes primary involvement of the meninges, and **encephalitis** indicates brain parenchymal involvement. However, these anatomic boundaries may be indistinct during infection, and many patients have clinical or imaging evidence of both meningeal and parenchymal involvement. So terms such as *meningoencephalitis* may better describe diffuse infections of the CNS by pathogens such as viruses. Brain abscess is the most common example of a focal infection of the CNS.

Q3/ HOW WOULD YOU DIAGNOSE CNS INFECTION?

The diagnosis of CNS infection depends on a combination of:

- Imaging of the brain
- Testing the cerebrospinal fluid (CSF) by culture, PCR and serologic methods
- In rare situations, biopsy of brain tissue is done.

Q4/ PROVIDES AN OVERVIEW OF THE TYPICAL CSF ABNORMALITIES WITH VARIOUS CNS INFECTIONS?

Table 643.1 Cerebrospinal Fluid Findings in Central Nervous System Disorders

CONDITION	PRESSURE (cm H_2O)	LEUKOCYTES (mm^3)	PROTEIN (mg/dL)	GLUCOSE (mg/dL)	COMMENTS
Normal	<28	<5, ≥75% Lymphocytes in neonates: <20	20-45	>50 (or 75% serum glucose)	
COMMON FORMS OF MENINGITIS					
Acute bacterial meningitis	Usually elevated	100-10,000 or more; usually 300-2,000; PMNs predominate	Usually 100-500	Decreased, usually <40 (or <50% of serum glucose)	Organisms usually seen on Gram stain and isolated by culture or identified by PCR
Partially treated bacterial meningitis	Normal or elevated	5-10,000; PMNs usual, but mononuclear cells may predominate if pretreated for extended period	Usually 100-500	Normal or decreased	Organisms may be seen on Gram stain. Pretreatment may render CSF sterile. PCR-based assays may detect bacterial DNA.
Viral meningitis or meningoencephalitis	Normal or slightly elevated	Rarely >1,000 cells. Eastern equine encephalitis and lymphocytic choriomeningitis may have cell counts of several thousand. PMNs early, but mononuclear cells predominate through most of the course,	Usually 50-200	Generally normal; may be decreased to <40 in some viral diseases, particularly mumps (15–20% of cases)	HSV encephalitis is suggested by focal seizures or by focal findings on MRI or CT scans or EEG. Most arboviruses detected by PCR of CSF or urine and serology.
UNCOMMON FORMS OF MENINGITIS					
Tuberculous meningitis	Usually elevated	10-500; PMNs early, but lymphocytes predominate through most of the course	100-3,000; may be higher in presence of obstruction	<50 in most cases; decreases with time if treatment is not provided	Acid-fast organisms rarely seen on smear. Large volumes of CSF required for recovery of organisms. *Mycobacterium tuberculosis* can be detected by PCR of CSF.

Acute Bacterial Meningitis Beyond the Neonatal Period

Bacterial meningitis is one of the most serious pediatric infections because it is associated with a high rate of acute complications and a risk of long-term morbidity and mortality. However, the use of antibiotics and vaccines against the most common causes of bacterial meningitis has significantly altered the spectrum of disease.

Q5/ WHAT ARE THE MOST COMMON CAUSES OF BACTERIAL MENINGITIS IN CHILDREN OLDER THAN 1 MONTH OF AGE?

- *Haemophilus influenzae* type b,
- *Streptococcus pneumoniae,*
- *Neisseria meningitidis.*

Q6/ NUMERTE THE MAJOR RISK FACTORS FOR BACTERIAL MENINGITIS?

- The lack of preexisting immunity to specific pathogens and serotypes reflected in a higher incidence of meningitis in young infants.
- Recent colonization with pathogenic bacteria
- Close contact with individuals having invasive disease caused by *N. Meningitidis* or *H. Influenzae*type b, (household, daycare centers, college dormitories, military barracks)
- Crowding,
- Poverty
- Male sex.

Q7/ WHAT IS THE MODE OF TRANSMISSION OF THESE PATHOGENS?

Through contact with respiratory tract secretions or droplets.

Q8/WHAT ARE THE PROPABLE CUASES OF RECURRENT OR LETHAL MENINGITIS?

1. Defects of the complement system (C5-C8) are associated with recurrent meningococcal infection.
2. Defects of the properdin system are associated with a significant risk of lethal meningococcal disease.
3. Splenic dysfunction (e.g., in sickle cell anemia) or asplenia (caused by trauma or a congenital defect) is associated with an increased risk of pneumococcal, *H. influenzae* type b, and meningococcal sepsis and meningitis.
4. T-lymphocyte defects (congenital or acquired by chemotherapy, AIDS, or malignancy) are associated with an increased risk of *Listeria monocytogenes* infections of the CNS.
5. The risk of pneumococcal meningitis is increased in children with congenital or acquired CSF leak across a mucocutaneous barrier, such as a lumbar dural sinus, cranial or midline facial defects (cribriform plate), fistulas of the middle ear or inner ear (oval window, internal auditory canal, cochlear aqueduct), or CSF leakage as a result of basilar or other skull fracture.
6. The risk of pneumococcal bacterial meningitis was historically increased by more than 30-fold in children with cochlear implants.
7. Lumbosacral dermal sinus and myelomeningocele are associated with staphylococcal, anaerobic, and gram-negative enteric bacterial meningitis.
8. CSF shunt infections increase the risk of meningitis caused by *Pseudomonas aeruginosa, Staphylococcus* spp. (*S. aureus* and coagulase-negative species.

STREPTOCOCCUS PNEUMONIAE

Although the incidence of pneumococcal meningitis has been reduced, *S. pneumoniae* remains the most frequently identified pathogen from cases of bacterial meningitis.

Q9/ NUMERSTE RISK FACTORS FOR STREPTOCOCCUS PNEUMONIA MENINGITIS?

1. Children with anatomic or functional asplenia secondary to sickle cell disease
2. Those infected with HIV have infection rates that are 20-to 100-fold higher than those of healthy children in the first 5 years of life.
3. Infections with endocarditis, otitis media, mastoiditis, sinusitis, pneumonia
4. CSF otorrhea or rhinorrhea
5. the presence of a cochlear implant
6. Immunosuppression.

NEISSERIA MENINGITIDIS

Six serogroups of meningococcus (A, B, C, X, Y, and W-135) are responsible for invasive disease in humans. Meningococcal cases are more common in the winter and spring, likely because of associations with viral infections, including influenza.

Nasopharyngeal carriage of *N. meningitidis* occurs in up to 15% of adults. Most infections in children are acquired from contact in a daycare facility, a colonized adult family member, or an ill patient with meningococcal disease. Colonization may last weeks to months. Children under 5 years of age have the highest rates of meningococcal infection, and a second peak in incidence occurs in persons between 15 and 24 years of age.

HAEMOPHILUS INFLUENZAE TYPE B

Invasive infections occurred primarily in infants 2 months to 2 years of age, the peak incidence was at 6-9 months, and 50% of cases occurred in the first year of life. The risk to children was markedly increased among household or daycare contacts of patients with *H. influenzae* type b disease.

Global vaccination efforts have also led to remarkable declines in the incidence of this disease. Incompletely vaccinated individuals, those in underdeveloped countries who are not vaccinated, and those with immune-compromising conditions remain at risk for *H. influenza* type b meningitis. Other serotypes of *H. influenzae* (a, f) have been associated with meningitis.

Q10/ WHAT ARE THE CLINICAL MANIFESTATIONS OF BACTERIAL MENINGITIS?

First: the onset of bacterial meningitis?

The onset of acute meningitis has two predominant patterns:

I/ Most often, meningitis is preceded by several days of fever accompanied by upper respiratory tract or, less often, gastrointestinal symptoms, followed by nonspecific signs of CNS infection, such as lethargy and irritability.

II/ Fortunately, the more dramatic presentation is less common and features sudden and progressive shock, purpura, disseminated intravascular coagulation, and reduced levels of consciousness, often resulting in progression to coma or death within 24 hours.

Second: The signs and symptoms of meningitis?

1. **Nonspecific findings include** fever, anorexia or poor feeding, headache, upper respiratory symptoms, myalgia, arthralgia, tachycardia, hypotension, and various cutaneous signs, such as petechiae, purpura, or an erythematous macular rash. The rash of meningococcemia is typified by an initial petechial rash that evolves into ecchymotic and purpuric lesions.
2. **Meningeal irritation** is manifested as nuchal rigidity, back pain, **Kernig sign** (flexion of the hip 90 degrees with subsequent pain upon extension of the leg), and **Brudzinski sign** (involuntary flexion of the knees and hips after passive flexion of the neck while supine).
3. **Seizures** (focal or generalized) related to cerebritis, infarction, or electrolyte disturbances occur in 20–30% of patients with meningitis. Seizures that occur on presentation or within the first 4 days of onset usually are of little prognostic significance. Poorer prognosis is suggested when seizures persist after the fourth day of illness, as these can be refractory to treatment.
4. **Alteration in mental status** is 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.
5. **Additional manifestations of meningitis** include photophobia and tache cerebrale, elicited by stroking the skin with a blunt object and observing a raised red streak within 30-60 seconds.

Q11/What are the signs of Increased ICP?

- Headache,
- Emesis,
- Bulging fontanelle or diastasis (widening) of the sutures,
- Cranial nerve palsy like oculomotor (anisocoria, ptosis) and abducens nerve paralysis,
- Hypertension with bradycardia, apnea, or hyperventilation,
- Decorticate or decerebrate posturing,
- Stupor, coma.
- Papilledema is more common in complicated meningitis and is suggestive of a chronic process, such as the presence of an intracranial abscess, subdural empyema, or occlusion of a dural venous sinus.

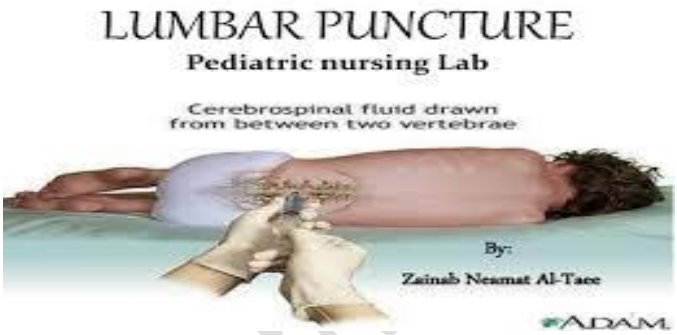
YOU SHOULD NOTE THAT:

- In children, particularly in those younger than 12-18 months, Kernig and Brudzinski signs are not consistently present.
- Focal neurologic signs usually are a result of vascular occlusion.
- Cranial neuropathies of the ocular, oculomotor, abducens, facial, and auditory nerves may also result from focal inflammation.
- Overall, 10–20% of children with bacterial meningitis have focal neurologic signs.

DIAGNOSIS

Q12/IN ORDER TO DIAGNOSE MENINGITIS YOU NEED TO OBTAIN CSF THROUGH LP, WHAT THE TESTS OF THE CSF SHOULD BE SENT?

CSF for *Gram stain and culture* is the most important step in the diagnosis of meningitis. Testing of the CSF for **neutrophilic pleocytosis, elevated protein, and/or reduced glucose concentrations** can yield results within a few hours and can indicate **bacterial** meningitis.



Q13/ WHEN IS LUMBER PUNCTURE (LP) CONTRAINDICATED?

1. Evidence of increased ICP (other than a bulging fontanel), such as third or sixth cranial nerve palsy with a depressed level of consciousness, or the Cushing reflex (hypertension and bradycardia associated 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.
3. Infection of the skin overlying the site of the LP.
4. Thrombocytopenia is a relative contraindication for LP.

If LP is delayed, empiric antibiotic therapy should be initiated.

Some clinicians obtain a head CT scan before LP to evaluate for evidence of increased ICP because an LP in the setting of elevated ICP may promote brain herniation. However, a head CT scan may delay diagnosis of meningitis and initiation of antimicrobials, and it does not always rule out increased ICP. Therefore, **head CT scans before LP are not routinely recommended** unless the patient has clinical signs or is at risk for elevated ICP or prior neurosurgical procedures including shunt placement. However, if a CT scan is to be obtained before LP, antimicrobial therapy should not be delayed.

Q14/ WHAT OTHER TESTS YOU CAN SEND FOR DIAGNOSIS OF MENINGITIS?

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 C-reactive protein, erythrocyte sedimentation rate, and procalcitonin can be seen in both bacterial and viral meningitis, but some clinical prediction tools include these tests to determine risk for bacterial meningitis.

Q15/ WHAT ARE THE CSF FINDINGS IN BACTERIAL MENINGITIS?

The CSF leukocyte count in bacterial meningitis often is elevated to >1,000/mm3 and, typically, there is a neutrophilic predominance (75–95%).

Turbid CSF is observed when the leukocyte count exceeds 200-400/mm3.

Healthy neonates may have as many as 20 leukocytes/ mm3, but older children without viral or bacterial meningitis have <8 leukocytes/mm3 in the CSF, and these should be nearly all lymphocytes or monocytes.

The CSF leukocyte count is <250/mm3 in as many as 20% of patients with acute bacterial meningitis. Pleocytosis may be absent in patients with severe overwhelming sepsis associated with meningitis; this is a poor prognostic sign.

Of note, neutrophilic pleocytosis may be present in the early stages of acute viral meningitis. The shift to lymphocytic-monocytic predominance in viral meningitis invariably occurs within 8-24 hours of an initial LP.

Pleocytosis with a predominance of neutrophils, an elevated protein level, and a reduced concentration of CSF glucose will usually persist for several days after initiation of appropriate parenteral antibiotics. Therefore, despite negative cultures, the presumptive diagnosis of bacterial meningitis can be made on the basis of an abnormal CSF cell count, protein, and glucose.

A traumatic LP may also complicate the interpretation of CSF tests, as CSF leukocyte count, and protein concentration are significantly affected by blood in the sample. However, the Gram stain, culture, and glucose level are unlikely to be influenced by blood in a CSF sample.

Q16/ WHAT ARE THE DIFFERENTIAL DIAGNOSIS OF BACTERIAL MENINGITIS?

- *Tuberculosis, Treponema Pallidum* (Syphilis)
- Fungi, such as (*Coccidioides, Histoplasma,* And*blastomyces*) in compromised hosts (*Candida, Cryptococcus,* And *Aspergillus*)
- Parasites, Such as *Toxoplasma Gondii*
- Viruses
- Focal infections (brain abscess and Para meningeal abscess; subdural empyema and spinal epidural abscess).
- Noninfectious illnesses include malignancy (lymphoma), immunologic diseases (vasculitis, sarcoidosis, autoimmune encephalitis)
- Exposure to toxins.

TREATMENT (antibiotic +steroid)

Q17/ WHAT IS THE INITIAL (EMPIRIC) ANTIBIOTIC THERAPY IN BACTERIAL MENINGITIS?

1) The initial (empiric) choice of antibiotic therapy for meningitis in immunocompetent infants and children beyond the neonatal period is**: Third-generation cephalosporin (ceftriaxone) plus vancomycin**. Third-generation cephalosporin's are sensitive to S. *pneumoniae, N. meningitidis,* and *H. influenzae* type b, ceftriaxone. Vancomycin is also recommended as part of empiric therapy due to cephalosporin-resistant strains of *S. pneumoniae,*
2) Patients allergic to penicillin and cephalosporin antibiotics can be treated with meropenem (40 mg/kg/dose every 8 hours); other alternatives include fluoroquinolones or chloramphenicol, if available.
3) If *L. monocytogenes* infection is suspected, as in young infants or those with a T-lymphocyte deficiency, ampicillin (300 mg/kg/day, divided every 6 hours) or iv. trimethoprim-sulfamethoxazole is an alternative treatment.
4) In immunocompromised patient, and gram-negative bacterial meningitis: cefepime or meropenem

Q18/ FOR HOW LONG THE ANTIBIOTIC THERAPY SHOHLD BE CONTINUED?

Currently, the recommended treatment duration

1) Uncomplicated *S. pneumoniae* meningitis is 10-14 days.
2) *N. meningitidis* meningitis, the recommended treatment duration 5-7days.
3) Uncomplicated *H. influenzae* type b meningitis should be treated for 7-10 days.
4) Gram-negative bacillary meningitis should be treated for 3 weeks, or at least 2 weeks after CSF sterilization,

Q19/ WHAT ARE THE COMMON SIDE EFFECTS OF ANTIBIOTIC THERAPY FOR MENINGITIS?

Phlebitis, drug fever, rashes, emesis, oral or vaginal candidiasis, and diarrhea. Ceftriaxone may cause reversible gallbladder pseudolithiasis.

Note: The CSF in most cases will be sterile within 24-48 hours of initiation of appropriate antibiotic therapy.

Table 643.4 Antibiotics Used for the Treatment of Bacterial Meningitis*

	NEONATES (TERM)		
DRUGS	**0-7 DAYS**	**8-28 DAYS**	**INFANTS AND CHILDREN**
Amikacin†‡	15 divided q24h	18 divided q24h	15-22.5 divided q8h, q12h, or q24h
Ampicillin	300 divided q8h	300 divided q6h	300-400 divided q4h, max 12 g/day
Cefepime	100 divided q12h	100 divided q12h	150 divided q8h, max 6 g/day
Ceftriaxone§	—	—	100 divided q12h or q24h. max 4 g/day
Ceftazidime	100 divided q12h	150 divided q8h	150-200 divided q8h, max 6 g/day
Gentamicin†‡	4 divided q24h	5 divided q24h	7.5 divided q8h
Meropenem	60 divided q8h	90 divided q8h for days 14-28	120 divided q8h, max 6 g/day
Nafcillin	75 divided q8h	100 divided q6h	200 divided q4h-q6h, max 12 g/day
Penicillin G	450,000 divided q8h	500,000 divided q6h	300,000-400,000 divided q4h, max 24 million U/day
Rifampin	—	10 q24h	15-20 divided q12h or q24h, max 600 mg/day
Tobramycin†‡	4 divided q24h	5 divided q24h	7.5 divided q8h
Vancomycin†‡#	40 divided q12h	60 divided q8h	age 3 mo-12: 60-80 divided q6h age >12 yr: 60-70 divided q6h-q8h

*Dosages in mg/kg (units/kg for penicillin G) per day.

†Smaller doses and longer dosing intervals, especially of aminoglycosides and vancomycin for very low-birthweight neonates, may be advisable.

‡Monitoring of serum levels is recommended to ensure safe and therapeutic values.

§Use in neonates is not routinely recommended because of inadequate experience in neonatal meningitis and concerns of displacement of bilirubin from albumin, leading to worsening of hyperbilirubinemia. Some centers use ceftriaxone in term neonates older than 7 days of age who are not receiving calcium-containing solutions or total parenteral nutrition and have normal albumin level and total serum bilirubin <5 mg/dL.

#Goal vancomycin AUC/MIC of 400-600 mg*hr/L or trough of 15-20 mg/L.

Adapted from Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis*. 2004;39:1267–1284. Table 6; with updated data from Kimberlin DW, Barnett ED, Lynfield R, et al. Red Book (2021): Report of the Committee on Infectious Diseases, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021.

Q20/ WHAT IS THE ROLE OF CORTICOSTEROIDS IN TREATING BACTERIAL MENINGITIS?

Rapid killing of bacteria in the CSF by the host's immune response and antibiotics leads to release of inflammatory agents (e.g., endotoxin) that precipitate a cytokine-mediated inflammatory cascade. The resultant edema and neutrophilic infiltration may aggravate neurologic injury with worsening of CNS signs and symptoms. Therefore, agents that restrain production of inflammatory mediators could be of benefit in bacterial meningitis.

Steroids reduced hearing loss in children with meningitis caused by *H. influenza* type b but not by other pathogens. The use of adjunctive steroids in children did not reduce mortality. These data support the use of intravenous dexamethasone 0.15 mg/kg/dose given every 6 hours for 2 days in the treatment of *H. influenzae* type b meningitis in children over 6 weeks of age. Corticosteroids appear to have maximum benefit if given 1-2 hours before antibiotics are initiated, which is difficult to operationalize; steroids may also be effective if given concurrently with or soon after the first dose of antibiotics.

Q21/ WHEN TO REPEAT CSF EXAMINATION SHOULD BE CONSIDERED?

1) neonates
2) patients with meningitis from gram-negative bacilli
3) β-lactam– resistant S. pneumoniae.

Q22/ NAME THE MOST COMMON ACUTE COMPLICATIONS OF BACTERIAL MENINGITIS?

1) Seizures
2) Increased ICP
3) Cranial nerve palsies
4) Stroke
5) Cerebral or cerebellar herniation
6) SIADH,
7) Thrombosis of dural venous sinuses.
8) Collections of fluid in the subdural space.

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, or abnormal results of cranial transillumination. CT or MRI scanning can confirm the presence of subdural effusion. In the presence of increased ICP or depressed level of consciousness, symptomatic subdural effusion should be treated by aspiration through the open fontanel. Fever alone is not an indication for aspiration.

SIADH occurs in some patients with meningitis, resulting in hyponatremia and reduced serum osmolality. This may exacerbate cerebral edema or result in hyponatremic seizures.

Q23/ WHEN DOES THE FEVER OF BACTERIL MENINGITIS USUALLY RESOLVED? WHAT ARE THE CAUSES OF PERSISTANT FEVER?

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 related to: Intercurrent viral infection, Nosocomial or secondary bacterial infection, thrombophlebitis or drug reaction. In meningitis caused by *N. meningitidis,* pericarditis or arthritis may occur during treatment.

Q24/ WHAT ABOUT THE PROGNOSIS OF BACTERIAL MENINGITIS?

Appropriate antibiotic therapy and supportive care have reduced the mortality rate of bacterial meningitis beyond the neonatal period to under 10%. The highest mortality rates are observed with pneumococcal meningitis. Severe neurodevelopmental sequelae may occur in 10–20% of patients recovering from bacterial meningitis.

Q25/ WHAT ARE THE POOR PROGNOSTIC FACTORS IN BACTERIAL MENINGITIS?

- Infants under 6 months of age.
- Those with high CSF bacterial burden.
- Those with seizures occurring later than 4 days into therapy.
- Those with coma or focal neurologic signs on presentation.

Q26/ WHAT ARE THE LONG TREM SEQUALAE OF BACTERIAL MENINGITIS?

1) The most common neurologic sequelae include:
2) Hearing loss,
3) Cognitive impairment
4) Recurrent seizures,
5) Delay in acquisition of language,
6) Visual impairment,
7) Behavioral problems.

Sensorineural hearing loss is most frequently detected and is often already present at the time of initial presentation. It results from cochlear or auditory nerve inflammation and occurs in as many as 30% of patients with pneumococcal meningitis, 10% with meningococcal meningitis, and 5–20% of those with *H. influenzae* type b meningitis. All patients with bacterial meningitis should undergo careful audiologic assessment before or soon after discharge from the hospital. Frequent reassessment in the outpatient setting is indicated for patients who develop a hearing deficit.

PREVENTION

Q27/ WHAT ARE THE PREVENTIVE MEASURES IN BACTERIAL MENINGITIS?

In Neisseria meningitidis: Rifampin 15-20 mg/kg/dose every 12 hours (maximum dose 600 mg) for 2 days as soon as possible. Alternative options include intramuscular ceftriaxone (125 mg once for children under age 15 years, or 250 mg once for persons older than 15 years) or ciprofloxacin 20 mg/kg as a single oral dose (maximum 500 mg).

For all close contacts of patients with meningococcal meningitis, regardless of age or immunization status.

In 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.

Many countries have included quadrivalent conjugate meningococcal vaccine (types A, C, Y, and W-135) as part of routine immunization schedules.

Vaccination is also recommended for persons 2 months to 18 years of age who are at increased risk for meningococcal disease, including those with anatomic or functional asplenia or complement deficiencies.

Haemophilus influenzae Type b: Rifampin 20 mg/kg/day (maximum dose 600 mg) given once daily for 4 days.

For all household contacts of patients if any close family member younger than 48 months has not been fully immunized or if an immunocompromised child of any age resides in the household.

All children should be immunized with *H. influenzae* type b conjugate vaccine beginning at 2 months of age.

Streptococcus pneumoniae: Antibiotic prophylaxis should not be administered to contacts of children diagnosed with pneumococcal meningitis.

Routine administration of pneumococcal conjugate vaccine is recommended for children under 5 years of age.

Vaccine given at 2 months of age in children who are at high risk for invasive pneumococcal infection, including those with functional or anatomic asplenia (including sickle cell disease), cochlear implants, CSF leaks, chronic illnesses (chronic heart disease, chronic lung disease, or diabetes mellitus),and underlying immunodeficiency (such as infection with HIV,primary immunodeficiency, and those receiving immunosuppressive therapy) should receive pneumococcal conjugate vaccine and the 23-valentpneumococcal polysaccharide vaccine (PPSV23).

TUGERCULOUS MENINGITIS

Tuberculous meningitis usually arises from the formation of a metastatic caseous lesion in the cerebral cortex or meninges that develops during the lymphohematogenous dissemination of the primary infection. It is the most serious complication in children.

EPIDIOMOLOGY:

- Tuberculous meningitis complicates approximately 0.3% of untreated TBIs in children.
- It is most common in children 6 months to 4 years old.
- Occasionally, tuberculous meningitis occurs many years after the infection, when rupture of one or more of the subependymal tubercles discharges tubercle bacilli into the subarachnoid space.

PATHOPHYSIOLOGY

- This initial lesion increases in size and discharges small numbers of tubercle bacilli into the subarachnoid space. The resulting gelatinous exudate infiltrates the corticomeningeal blood vessels, producing inflammation, obstruction, and subsequent infarction of the cerebral cortex.
- The brainstem is often the site of greatest involvement, which accounts for the commonly associated dysfunction of cranial nerves III, VI, and VII.
- The exudate also interferes with the normal flow of cerebrospinal fluid (CSF) in and out of the ventricular system leading to a communicating hydrocephalus.
- Profound abnormalities in electrolyte metabolism from salt wasting or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) also contribute to the pathophysiology of tuberculous meningitis.

CLINICAL MANEFESTATIONS

The clinical progression of tuberculous meningitis may be rapid or gradual.

Rapid progression tends to occur more often in infants and young children, who can experience symptoms for only several days before the onset of acute hydrocephalus, seizures, and cerebral edema.

More often, the signs and symptoms progress slowly over weeks and are divided into three stages.

- The first stage typically lasts 1-2 weeks and is characterized by nonspecific symptoms such as fever, headache, irritability, drowsiness, and malaise. Focal neurologic signs are absent, but infants can experience stagnation or loss of developmental milestones.

- The second stage usually begins more abruptly. The most common features are lethargy, nuchal rigidity, seizures, positive Kernig and Brudzinski signs, hypertonia, vomiting, cranial nerve palsies, and other focal neurologic signs. The accelerating clinical illness usually correlates with the development of hydrocephalus, increased intracranial pressure, and vasculitis. Some children have no evidence of meningeal irritation but can have signs of encephalitis, such as disorientation, movement disorders, or speech impairment.

- The third stage is marked by coma, hemiplegia or paraplegia, hypertension, decerebrate posturing, deterioration of vital signs, and eventually death.

It is imperative that antituberculosis treatment be considered for any child who develops:

Basilar meningitis and hydrocephalus, cranial nerve palsy, or stroke with no other apparent etiology.

Often the key to the correct diagnosis is identifying an adult who has infectious TB and is in contact.

with the child. Because of the short incubation period of tuberculous meningitis, the illness has not yet been diagnosed in adults in many cases.

DIAGNOSIS

The diagnosis of tuberculous meningitis can be difficult early in its course, requiring a high degree of suspicion on the part of the clinician.

- The TST is nonreactive in up to 50% of cases,
- 20–50% of children have a normal chest radiograph.
- **SOOOOO** The most important laboratory test for the diagnosis of tuberculous meningitis is examination and culture of the lumbar CSF.

1) The CSF leukocyte count usually ranges from 10 to 500 cells/μL. PMNs may be present initially, but lymphocytes predominate in the majority of cases.
2) The CSF glucose is typically <40 mg/dL but rarely <20 mg/dL.
3) The protein level is elevated and may be extremely high (400-5,000mg/dL) secondary to hydrocephalus and spinal block.
4) Microscopic examination of acid-fast–stained CSF and mycobacterial culture of large-volume lumbar CSF (up to 15 mL)

- Polymerase chain reaction (PCR) testing of the CSF and ADA levels can improve the diagnosis.
- IGRA in the evaluation of healthy young children ≥2 years of age
- Cultures of other body fluids can help confirm the diagnosis.
- Radiographic studies can aid in the diagnosis of tuberculous meningitis.

NOTE: During early stage, the CSF can resemble that of viral aseptic meningitis, only to progress to the more severe CSF profile over several weeks.

BRAIN IMAGING

- CT or MRI of the brain of patients with tuberculous meningitis may be normal during early stages of the disease.
- As the disease progresses, basilar enhancement and communicating hydrocephalus with signs of cerebral edema or early focal ischemia are the most common findings.
- Some young children with tuberculous meningitis have one or several clinically silent tuberculomas, occurring most often in the cerebral cortex or thalamic regions a tumor-like mass resulting from aggregation of caseous tubercles that usually manifests clinically as a brain tumor, often infratentorial, located at the base of the brain near the cerebellum.

TREATMENT

The initial treatment regimen includes isoniazid, rifampin, pyrazinamide, and ethambutol. The ethambutol can be discontinued once the organism is known to be susceptible to the other first-line drugs. Pyrazinamide is discontinued after 2 months.

isoniazid and rifampin are continued for an additional for 9-12 months. In addition to corticosteroid in the first few weeks of treatment.

Ventriculoperitoneal shunting in CNS disease may be necessary adjuncts to medical therapy.

PROGNOSIS

The prognosis of tuberculous meningitis correlates most closely with the clinical stage of illness at the time treatment is initiated. The majority of patients in the first stage have an excellent outcome, whereas most patients in the third stage who survive have permanent disabilities, including blindness, deafness, paraplegia, diabetes insipidus, or mental retardation. The prognosis for young infants is generally worse than for older children.

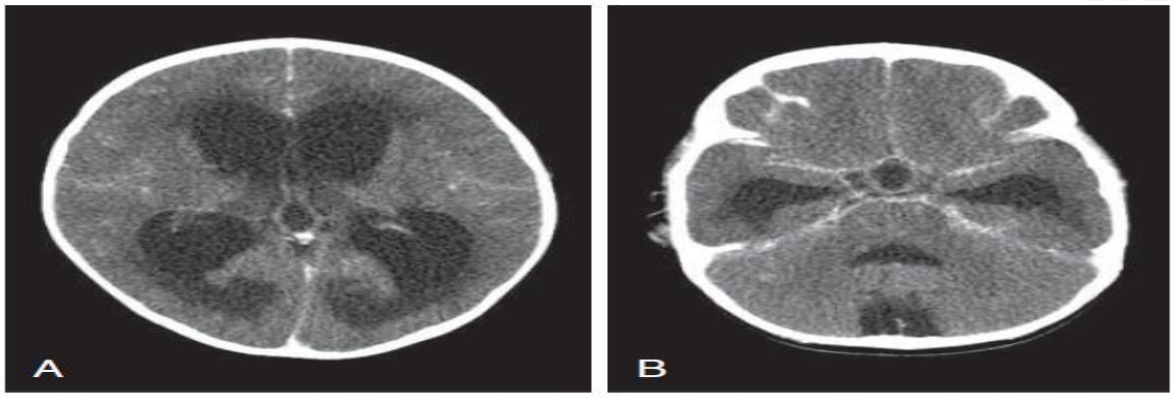


Fig. 261.16 Tuberculous meningitis in a child. A and B, Postcontrast CT images demonstrate intense enhancement in the suprasellar cistern, sylvian cistern, and prepontine cistern. Dilation of the ventricular system is seen, consistent with associated hydrocephalus. *(From Lerner A, Rajamohan A, Shiroishi MS, et al. Cerebral infections and inflammation. In Haaga JR, Boll DT, eds. CT and MRI of the Whole Body, 6th ed. Philadelphia: Elsevier; 2017: Fig 10-20.)*

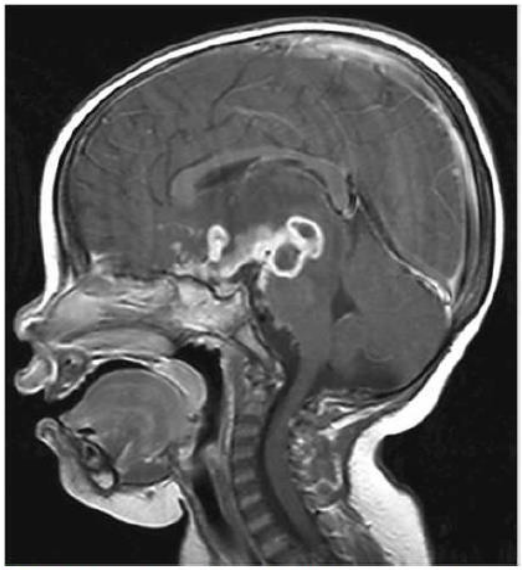


Fig. 261.17 MRI of brain of 3-yr-old child showing multiple pontine tuberculomas.

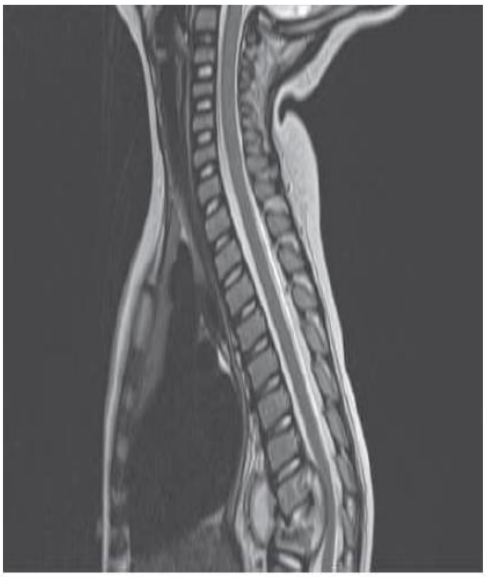


Fig. 261.18 Tuberculosis of the spine in a toddler. *(From Feder HM Jr, Rigos L, Teti K. Pott's disease in a Connecticut toddler. Lancet. 2016;388:504–505.)*

Viral Meningoencephalitis

Viral meningoencephalitis is an acute inflammatory process involving the meninges and/or brain parenchymal tissue. These infections are caused by a number of different pathogens, and quite often, no pathogen can be identified from the CSF or brain tissue specimens after routine clinical testing. Viral meningoencephalitis is the most common cause of CNS infection.

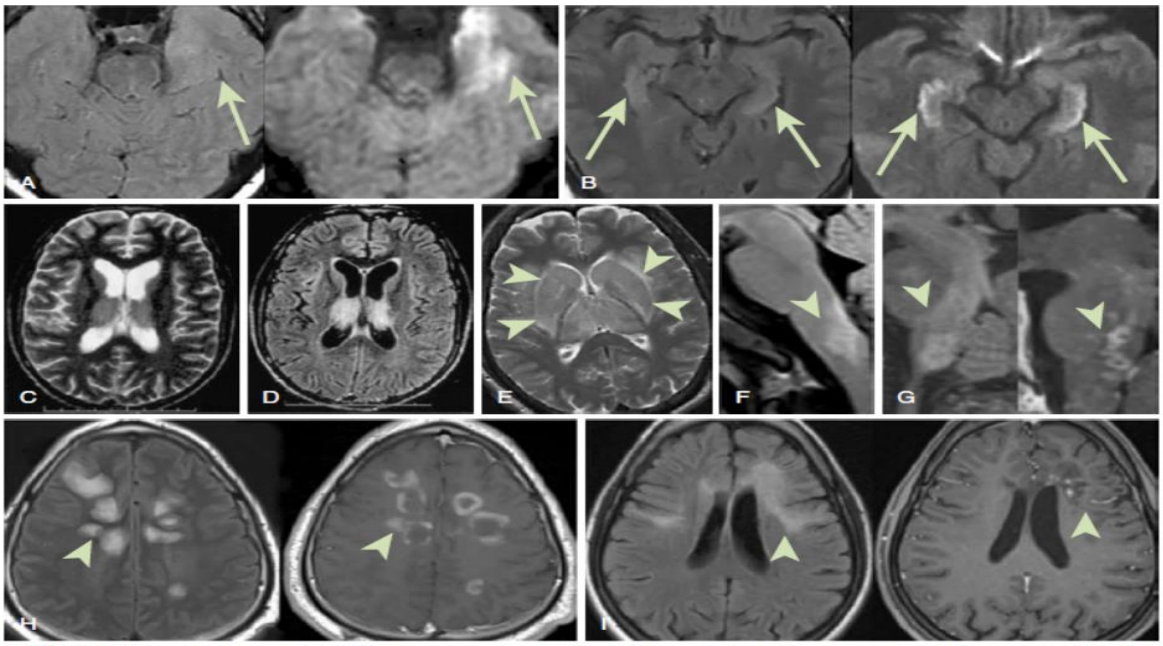


Fig. 643.1 MRI findings in acute encephalitis. Representative images from infectious and autoimmune encephalitides are shown. **A**, Early herpes simplex encephalitis; left temporal lobe abnormalities are more clearly seen on diffusion-weighted imaging (DWI) *(right)* than fluid-attenuated inversion recovery (FLAIR) *(left)*. **B**, Autoimmune limbic encephalitis; bilateral mesial temporal lobe abnormalities seen on both DWI *(right)* and FLAIR *(left)*—note the symmetric nature of the lesions. **C-E**, Arboviral encephalitis; T2-weighted image of a patient with Japanese encephalitis shows hyperintensities in bilateral thalamus **(C)**. The hyperintensities are better visualized in FLAIR image **(D)**. T2-weighted image of patient with **(E)** Eastern equine encephalitis shows increased signal intensity and swelling in the deep gray matter. **F**, Neuromyelitis optica; FLAIR image of a patient who presented with brainstem encephalitis and found to have antibodies to aquaporin-4. **G**, *Listeria* brainstem encephalitis; FLAIR *(left)* and post-gadolinium *(right)* images show T2 abnormalities similar to neuromyelitis optica (NMO) but also multiple rim-enhancing brainstem lesions typical of *Listeria*. **H**, In acute disseminated encephalomyelitis, multifocal areas of T2 hyperintensity are seen on FLAIR *(left)* with characteristic incomplete rims of enhancement after gadolinium administration *(right)*. **I**, In myelin oligodendrocyte glycoprotein encephalomyelitis, multifocal and confluent lesions can be seen on FLAIR imaging *(left)*, and post-gadolinium imaging *(right)* shows patchy areas of enhancement. *(A, B, and F-H, Modified from Venkatesan A, Michael BD, Probasco JC, et al. Acute encephalitis in immunocompromised adults. Lancet. 2019;393:702–716, Fig. 1, p. 709; C and D, Modified from Misra UK, Kalita J, Phadke RV, et al. Usefulness of various MRI sequences in the diagnosis of viral encephalitis. Acta Trop. 2010;116[3]:206–211, Fig 1ab; E, From Harvala H, Bremner J, Kealey S, et al. Case report: Eastern equine encephalitis virus imported to the UK. J Med Virol. 2009;81[2]:305–308; I, Courtesy Dr Michael Levy, Harvard Medical School.)*

ETIOLOGY

- ***Enteroviruses***: the most common causes of viral meningoencephalitis.

(poliovirus, coxsackievirus, enterovirus, and echovirus) It is spread directly from person to person; the disease ranges from mild, self-limited illness to severe encephalitis resulting in death or significant sequelae.

- ***Parechoviruses:*** is often self-limited but can be severe in neonates or immunocompromised hosts. They are an important cause of meningoencephalitis in infants and rarely cause disease in older children. Its manifestations are similar to those of enteroviruses with the exception that it may exhibit abdominal signs or sepsis-like syndrome as well as more severe MRI lesions of cerebral cortex and at times an absence of CSF pleocytosis.
- ***Herpes simplex virus (HSV) type 1*** is an important cause of severe, sporadic encephalitis in children and adults, with progression to coma and death in 70% of cases without antiviral therapy. In neonates, severe encephalitis with diffuse brain involvement can be caused by ***HSV type 2***, transmitted vertically at delivery.
- ***Varicella-zoster virus (VZV)*** may cause CNS infection in a close temporal relationship with clinical manifestations of chickenpox. The most common manifestation of CNS involvement by VZV is cerebellar ataxia, whereas the most severe form is acute encephalitis. After primary infection, VZV establishes latency in spinal and cranial nerve roots and ganglia, and reactivation is evidenced by herpes zoster that can be accompanied by mild meningoencephalitis.
- ***Epstein-Barr virus*** is associated with various CNS syndromes.
- ***Cytomegalovirus (CMV)*** can occur with congenital infection or disseminated disease in immunocompromised hosts, but it is an exceptionally rare cause of meningoencephalitis in immunocompetent infants and children.
- ***Mumps*** can cause meningoencephalitis and has a higher incidence in regions where the mumps vaccine is not implemented. Mumps meningoencephalitis is typically mild, but deafness from damage of the eighth cranial nerve and subacute sclerosing panencephalitis (SSPE) can occur.
- **Others measles, rubella, respiratory viruses (adenovirus, coronaviruses, influenza virus, parainfluenza virus, respiratory syncytial virus), rotavirus, astroviruses, lymphocytic choriomeningitis virus, or rabies** are also associated with meningoencephalitis.
- Arboviruses are transmitted by arthropod vectors, typically mosquitoes or ticks. Most of these viral infections are considered zoonotic, as their primary reservoir is in birds or small animals; they include many viruses e.g., ***West Nile virus, zica.***
- ***HIV*** is associated with acute meningoencephalitis and can cause chronic encephalopathy leading to neurocognitive decline.
- In exceptionally rare situations, meningoencephalitis may follow live virus vaccination against polio, measles, mumps, rubella, or varicella.

EPIDEMIOLOGY:

Meningoencephalitis has a seasonal pattern, with a peak incidence in the summer and late fall caused by a spike in circulation of enteroviruses and arboviruses.

PATHOGENESIS AND PATHOLOGY

- Neurologic damage is caused by direct invasion and destruction of neural cells and tissues by actively multiplying viruses and by the host reaction to viral antigens. A marked degree of demyelination with preservation of neurons and their axons is considered to represent predominantly "post infectious" or autoimmune encephalitis.
- In HSV encephalitis, the cerebral cortex (classically the temporal lobes in HSV-1 infection) are often severely affected.
- Arboviruses tend to affect the entire brain.
- Rabies has a predilection for the basal structures.

CLINICAL MANIFESTATION:

- The clinical course resulting from infection with the same pathogen is widely variable. Some children may appear initially mildly affected, then lapse into coma and die suddenly. In others, the illness may be very severe followed by complete recovery.
- The onset of illness is generally acute.
- The presenting manifestations in older children are headache & hyperesthesia, whereas in infants, irritability & lethargy.
- Headache is most often frontal or generalized; adolescents frequently complain of retrobulbar pain.
- Fever, nausea and vomiting, photophobia, and pain in the neck, back, and legs are common.
- Altered mental status that progresses to encephalopathy in combination with uncontrolled body movements and seizures.
- Focal neurologic signs may be persistent, fluctuating, or migratory.
- loss of bowel and bladder control.
- Enteroviruses may cause anterior horn cell injury and acute flaccid paralysis.
- Exanthems can precede or accompany CNS signs, especially with enteroviruses, VZV, measles, rubella, and WNV.
- Specific conditions associated with CNS viral infection include Guillain-Barre syndrome, transverse myelitis, hemiplegia, and cerebellar ataxia.
- During the pandemic SARS-CoV-2, neurologic diseases were uncommonly associated with this infection in children, including encephalitis, Guillain-Barre syndrome, and stroke. In addition, in the multisystem inflammatory syndrome of children

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DIAGNOSIS

1/ CSF findings in viral meningoencephalitis are characterized by:

- ✓ a pleocytosis of leukocytes with counts typically <1,000/mm3. (In the initial hours of disease, the cells may be polymorphonuclear, whereas mononuclear cells predominate for the remainder of the illness)
- ✓ CSF protein concentration tends to be elevated, especially if brain destruction is extensive, as with HSV encephalitis.
- ✓ The glucose level is typically normal, although hypoglycorrhachia can occur with certain viruses (e.g., mumps).
- ✓ With Parechoviruses, the CSF glucose, protein, and cell counts may be normal.

2/ Identification of an infectious cause relies on analysis of the CSF for the presence of pathogens by PCR and serology

3/ EEG typically shows diffuse slow-wave activity, although focal changes in temporal regions can be observed in HSV meningoencephalitis.

4/ MRI of the brain may demonstrate focal brain lesions that correlate with clinical disease, including temporal lobe involvement to suggest HSV-1 disease. Hyperdense lesions may also be identified on T2 and FLAIR imaging.

Table 643.5 Laboratory Testing and Neuroimaging Characteristics of Selected Pathogens

	LABORATORY TESTING	CHARACTERISTIC BRAIN MRI FINDINGS
VIRUSES		
HSV	CSF PCR (false negative can occur in first 72 hours). PCR of skin lesions may also be helpful if they occur in conjunction with neurological disease. Blood PCR in neonates. In neonatal CNS disease, CSF PCR is completed near the end of therapy to guide final treatment duration.	For HSV-1: Asymmetric abnormalities in mesiotemporal lobes, orbitofrontal lobes, and insular cortex with edema, possible restricted diffusion or hemorrhage (late stage) HSV-2 in neonates can appear like HSV-1. In adults, HSV-2 meningitis has variable findings (including no abnormalities) or may mimic HSV-1 encephalitis.
Varicella-zoster virus	CSF PCR; skin lesion PCR, biopsy, or DFA for VZV	Could affect temporal lobes, similar to HSV-1; lesions can occur in cerebellum and brainstem; ischemic or hemorrhagic lesions in white matter or gray-white matter junction suggest vasculopathy
Enteroviruses	CSF PCR; Blood PCR; nasopharyngeal swabs can be difficult to interpret as asymptomatic rhino/enterovirus infections are frequently detected. Stool testing only recommended for epidemiological tracing, including for poliovirus or enterovirus D68.	Wide range of findings from normal to diffuse white matter changes. EV 71 causes lesions in the dorsal brainstem, dentate nuclei of cerebellum, and anterior horns of spinal cord. EV D68 often causes lesions of the brainstem, spinal cord with involvement of the central gray matter, and of anterior horn cells.
Parechoviruses	CSF PCR; blood PCR	Variable findings from normal to restricted diffusion of thalami, corpus callosum, subcortical, and periventricular white matter, predominating in the frontal and parietal regions.
Measles*	Serum IgG and IgM; PCR of nasopharyngeal, throat, or urine samples in early infection	Cerebral edema, multifocal lesions, can resemble ADEM in acute setting
Mumps*	CSF and serum IgM and IgG; PCR from throat swab	Lesions in brainstem, hippocampus, and splenium of corpus callosum

DIFFERENTIAL DIAGNOSIS

1. Bacterial meningitis, given the consequences if that disease is untreated. Most children with acute bacterial meningitis are more critically ill than those with viral infection (with HSV as an exception).
2. Brain abscess or subdural or epidural empyema, may have features similar to viral infections.
3. Infections caused by *m. Tuberculosis,* syphilis.
4. *Mycoplasma pneumoniae* has been suggested as a causative pathogen in meningoencephalitis, either as a direct pathogen or a trigger of post infectious symptoms.
5. Infections caused by fungi, rickettsia, protozoa, and other parasites.
6. Various noninfectious disorders may be associated with CNS inflammation include malignancy, autoimmune diseases, intracranial hemorrhage, and exposure to certain drugs or toxins.
7. Autoimmune encephalitis caused by anti–*N*-methyl-d-aspartate(anti-NMDA) receptor antibodies, disseminated encephalomyelitis (ADEM) may also initially be confused with encephalitis.

TREATMENT

For most causes of viral meningoencephalitis, no effective antiviral agents exist; therefore, treatment is primarily supportive care. Intravenous fluids are typically administered because of poor oral intake. NSAIDs are often used for symptomatic relief of headaches. Control of seizures, cerebral edema, disturbed fluid and electrolyte balance, aspiration, respiratory failure…

Members of the herpesvirus family can be treated with antivirals, with acyclovir, ganciclovir, cidofovir, and foscarnet, Parenteral acyclovir has been specifically shown to dramatically reduce morbidity and mortality rates in HSV-associated meningoencephalitis.

PROGNOSIS AND COMPLICATIONS

Some sequelae of infection may be subtle; therefore neurologic, developmental, and audiological evaluations should be part of the routine follow-up of children who have recovered from viral meningoencephalitis.

COMPLICATIONS:

- ✓ Motor incoordination
- ✓ Seizures
- ✓ Total or partial deafness
- ✓ Behavioral disturbances
- ✓ Visual disturbances from chorioretinopathy and perceptual amblyopia may also occur.

Recovery from viral infections of the CNS depends on the severity of the clinical illness, the specific causative agent, and the age of the child. If the clinical illness is severe and substantial parenchymal involvement is evident, the prognosis is poor.

Severe sequelae should also be anticipated in those with infection caused by HSV if it was not diagnosed and treated early in the disease.

PREVENTION

For some viruses that cause meningoencephalitis, vaccines are available for prevention. Widespread use of effective viral vaccines for polio, measles, mumps, rubella, and varicella has almost eliminated CNS complications from these diseases.

Control of vectors for some viral infections e.g., arboviruses by insecticides and eradicating insect breeding sites. Also minimizing mosquito and tick bites through the application of insect repellents on exposed skin and wearing long-sleeved shirts, long pants, and socks when outdoors, especially at dawn and dusk, reduces risk for arbovirus infection.